

MITTAGE

THIS MANUAL PRESENTS THE AUTHOR'S OBSERVATIONS
AND EXPERIMENTS ON MITE BORNE TYPHUS.

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PREFACE

This thesis presents the author's observations and experiments on the subject of mite borne typhus. Though this disease has been studied in a number of countries and a considerable volume of literature has resulted, particularly within the last decade, there are no reviews of the subject of any comprehensive nature. The author has therefore taken this opportunity to embody his own observations in a general account of the subject, which, it is hoped, will prove of some interest.

The subject matter has been arranged in Sections, each dealing with a particular aspect of the disease, and each terminating with a number of paragraphs under the heading "Conclusions". These "Conclusions" summarise the matter which has been dealt with in the preceding Section, and also present the author's own deductions.

The author wishes to express his indebtedness to Dr. R. Lewthwaite for the loan of original papers and translations, to Dr. S. R. Savor for a strain of rickettsiae and to the medical officers who sent pathological specimens for examination.

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SECTION 1

INTRODUCTION

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INTRODUCTION

The Typhus Group of Fevers

During the course of the present century a close connection has been found to exist between certain endemic diseases of world-wide occurrence, and typhus fever. These diseases, together with typhus itself, constitute what is known as "the typhus group of fevers".

The early history of typhus fever is obscure. It seems certain that the disease was known in ancient times, though early records of epidemic disease give very confused descriptions from which it is often impossible to differentiate between plague, typhus fever, typhoid fever, relapsing fever and other conditions.

In the sixteenth century Fracastoro gave the first clear description of typhus in his "De Contagione et Contagiosis Morbis", and distinguished the condition from plague, but little further progress was made in the elucidation of the nature of the major epidemic diseases for the next two and a half centuries. During this time accounts of adynamic, putrid, ataxic, typhus and gastro-enteric fevers became more numerous, and the name "typhus fever" was applied equally to typhoid and relapsing fevers as well as to typhus.

It was not till 1837 that Gerhard showed that typhoid fever was a distinct disease. A few years

later relapsing fever was recognised as a separate condition. Now, stripped of attributes belonging to other diseases, the clinical picture of typhus fever became clearly defined.

The remaining members of the typhus group of fevers, the "typhus-like fevers", as they are often collectively called, resemble typhus fever, and each other, in many respects, though each member of the group has its own peculiar features. In one fundamental respect especially, they differ from typhus fever itself, but resemble each other. Typhus fever is an epidemic disease, communicated directly from man to man in outbreaks which are often of considerable dimensions, while the typhus-like diseases are entirely endemic, and never show any evidence of transmission from one human being to another.

At the end of the last century only two examples of the typhus-like diseases were known: the spotted fever of the Rocky Mountains and the tsutsugamushi disease of Japan. To-day, the list of countries from which typhus-like diseases have been reported is long. At first the etiology of these diseases was obscure: their close connection with typhus fever was not at once evident. The conception of a disease group which includes epidemic typhus fever and also diseases of an endemic nature was evolved only gradually, as knowledge of the etiology and pathology of these conditions advanced.

Nevertheless, the clinical resemblances between these endemic diseases and typhus fever did not escape the notice of some of the earlier observers. The

tsutsugamushi disease of Japan was at one time regarded as a local form of typhus fever, though this view was later abandoned (Kitashima and Miyajima, 1918). The spotted fever of the Rocky Mountains, too, was thought by some observers to be a type of typhus fever. But the majority of workers considered these diseases and typhus fever to be quite distinct. The epidemiological features were such that any classification which grouped endemic diseases as types of typhus fever could not be accepted.

While the question of the exact nature of these diseases was still under discussion, the occurrence of conditions of a similar nature was being reported from a number of countries. In 1902 Schuffner (1915) noted a disease in Sumatra which he considered analogous to the tsutsugamushi disease; in 1904 the tsutsugamushi disease was observed in Formosa (Hatori, 1919); an apparently similar condition, originally described as "Mossman fever", was observed in Queensland, Australia (Smithson, 1910); and Megaw (1917) described a fever which he himself had suffered from in India, and which he considered similar to Rocky Mountain spotted fever.

At the same time important researches into the etiology and pathology of typhus fever were proceeding. Nicolle (1909) showed that the blood of patients suffering from typhus fever, taken during the febrile period and also immediately before and afterwards, was infective for chimpanzees. A febrile illness resulted which was practically identical with the disease in

man, and the blood of infected animals was again infective for fresh monkeys. The mode of transmission of typhus fever was also demonstrated by Nicolle and his colleagues. They showed that body lice which had sucked the blood of infected chimpanzees could, by feeding on fresh animals, transmit the disease to them (Nicolle et al., 1909).

Ricketts (1909), in his researches on Rocky Mountain spotted fever, described the presence of minute diplococcoid bodies in the blood of men, monkeys and guineapigs suffering from this disease, and in certain ticks which were suspected of transmitting the condition. Suspensions of these bodies were agglutinated by the serum of recovered animals. Further, in lice which had fed on cases of typhus fever, Ricketts and Wilder (1910) recognised similar bodies. These findings were confirmed by Da Rocha-Lima and von Prowazek, Da Rocha-Lima (1916) giving an accurate description of the bodies, which he named *Rickettsia prowazeki*.

Meanwhile Rabinowitch (1912), Plotz et al. (1915) and other workers had advanced claims concerning micro-organisms which they had isolated from cases of typhus, each worker considering his organism to be the cause of the disease. These claims have now been invalidated, while the work of Arkwright, Bacot and Duncan (1919), Wolbach, Todd and Palfrey (1922), Atkin and Bacot (1922) and other investigators demonstrated such a constant association between the virus of typhus fever and the presence of rickettsiae in lice that it became generally accepted that the virus of the

disease was identical with the rickettsiae.

The position was now becoming much clearer. The same type of organism was the cause of both typhus fever and Rocky Mountain spotted fever, both diseases were transmitted by arthropoda and the pathology of the two diseases was essentially similar (Wolbach, 1916). Evidence accrued, too, to show that the tsutsugamushi disease was transmitted by an arthropod - in this case a larval mite - and a new type of typhus-like disease, transmitted by rat fleas, was discovered (Maxcy and Havens, 1923). In due course, rickettsiae were isolated from cases of these diseases.

The epidemiology of typhus fever and the typhus-like diseases could now be better comprehended. Typhus fever is an epidemic disease because the vector of infection, the body louse, is a parasite of man alone. Should it leave its human host, for whatever reason, the body louse always seeks another host of the same species. On the other hand, the arthropoda which transmit the typhus-like diseases are primarily parasites of rodents and other lower vertebrates. They attack man only when he comes into contact with these animals and do not spread from one human being to another. These lower animals form the natural reservoir of infection of the typhus-like diseases, in contra-distinction to man, who is himself the reservoir of typhus fever. A further point of importance is that animals infected with rickettsiae apparently suffer little ill-effect from this. Thus there is much less tendency for parasites to leave their animal host, than occurs for example in bubonic plague, in

which case the rat fleas leave the dying rat to find a new host, often man.

Another important advance which tended to emphasize still further the essential similarity in nature of typhus fever and the typhus-like diseases was the discovery of certain agglutinative properties of the serum of typhus fever patients. Wilson (1909, 1910) showed that the serum of these patients agglutinated suspensions of coliform bacilli which had been isolated from the urine, and Weil and Felix (1916) repeated Wilson's experiments using strains of *Proteus* which they had obtained in a similar manner. These strains they termed *Proteus* X, and found that one of them in particular, *Proteus* X19, was agglutinated by the sera of typhus patients in high dilutions. Another strain, *Proteus* X2, was also agglutinated, though not to such high titres.

Application of this test, the Weil-Felix reaction, to the typhus-like diseases showed that in all of them, with one exception, antibodies developed to the two types of *Proteus*, in varying degree. But the serum from cases of the tsutsugamushi disease in Japan and from cases of a similar condition in Malaya gave no such reaction. Fletcher and Lesslar (1926), however, showed that in "scrub typhus", a tsutsugamushi-like disease in Malaya, the serum of patients developed antibodies for a variant of *Proteus* X19, known as *Proteus* XK. Applied to the tsutsugamushi disease in Japan and to similar conditions elsewhere, this reaction was again found to be positive.

Thus the conception of the typhus group of

fevers was evolved. The causal organisms, the serum reactions and the pathology as well as the clinical picture of the various diseases of the group were all found to be closely related. In each case, too, the diseases were transmitted by arthropoda: lice, ticks, fleas, mites. In the light of these findings, fevers, particularly in the tropics, which had hitherto been regarded as of obscure nature were in many cases recognised as members of the typhus group of diseases. We know to-day that the distribution of the diseases of this group is very wide indeed. A summary of the main facts in relation to the various diseases of the group is given in Table 1.

Before proceeding further it is necessary to consider briefly the question of the classification of the typhus group of fevers. Two main schemes of classification exist, that of Megaw (1921) and that of Felix (1935). Others have been put forward but depend in the main on information utilised in the classifications just mentioned.

Megaw's classification depends on the transmitting arthropod vector, and three groups of diseases were at first recognised:-

1. Louse typhus
2. Tick typhus
3. Mite typhus

The scheme has since been amplified, and is now as shown in Table 2 (Megaw, 1934).

A classification which stresses epidemiological factors is of great practical value, since the control of the diseases of the typhus group is effected mainly

Table 1

Disease	Rickettsia	Distribution	Insect Vectors	Reservoir	Immunology
Louse borne typhus; Epidemic- exanthem- atic- or classical typhus, ship fever, jail fever.	<i>R. prowazeki</i>	Europe, Abyss- inia, N. & S. Africa, Belg- ian Congo, Asia Minor, Iran, China, Mexico, Peru, Chili.	<i>Pediculus humanis</i>	Man	Partial antigenic corres- pondence with flea borne typhus, but no immunolog- ical relationship to other diseases of the typhus group.
Flea borne typhus; Endemic- ship- ship- or tropical typhus, Hone's disease.	<i>R. mooseri</i> (<i>R. muricola</i>)	World-wide (See Table 3)	<i>Xenopsylla cheopis</i>	Rat	Related to louse borne typhus and other diseases of the group as above.
Mite borne typhus; tsutsugamushi dis- ease, Japanese river fever, Kedani fever, scrub typhus.	<i>R. orientalis</i>	See Sect. 11	See Sect. 1V	See Sect. 1V	All strains immunologic- ally identical, but no antigenic relationship to other diseases of the group.
Rocky Mountain spotted fever	<i>R. rickettsi</i>	U. S. A.	<i>Dermacentor andersoni</i> ; <i>D. variabilis</i>	Goats, hares, other small rodents	Partial antigenic corr- espondence with fievre boutonneuse; complete correspondence with Sao Paulo typhus; none with louse, flea or mite ty- phus, but quite probab- ly will be found relat- ed to other types of tick typhus.
Fievre boutonneuse	<i>R. rickettsi</i> var. <i>conori</i>	Mediterranean area	<i>Rhipicephalus sanguineus</i>	Dog	See above
South African tick typhus	<i>R. rickettsi</i> var. <i>pijperi</i>	South Africa, Kenya, Abyss- inia	<i>Haemaphysalis leachi</i> ; <i>R. san- guineus</i>	Dog	Probably corresponds with Rocky Mountain spotted fever, though at first thought quite distinct
Sao Paulo typhus	<i>R. rickettsi</i> var. <i>brasili- ensis</i>	South Brazil	<i>Amblyomma cajennense</i>	Opossum	See Rocky Mountain spotted fever
Q fever	<i>R. burneti</i> (<i>R. diaporica</i>)	Australia U. S. A.	<i>H. humerosa</i> <i>D. andersoni</i> <i>D. occidentalis</i> <i>A. americanum</i> <i>R. sanguineus</i>	Bandicoot	?

by measures directed towards these points. The more recent use of vaccines has in no way diminished the importance of such measures.

Felix (1935) proposed a classification based on the serological reactions which occur in the various diseases of the group (Table 3). The diseases fall into three groups, OX19, OXK and "type undetermined". In the first group are placed those conditions in which high titres are obtained with suspensions of *Proteus* OX19 and titres of low or moderate degree only with *Proteus* OX2 (only the 'O' variants are used in the Weil-Felix reaction: see also Section V). In the second group the serum from cases of the diseases there listed agglutinates suspensions of *Proteus* OXK only, while in the diseases of the "type undetermined" group low titres may be obtained with one or more of the three types of *Proteus* OX.

Felix considers that this classification rests fundamentally on an etiological basis, the results of the Weil-Felix reaction in each disease of the group depending on the antigenic structure of the rickettsia causing that disease. This relationship between the Weil-Felix reaction and the type of rickettsia depends on the fact that the 'O' antigen of *Proteus* OX19 is identical with part of the antigenic complex of *R. prowazeki* (Weil and Felix, 1921). It is assumed that the 'O' antigen of *Proteus* OXK corresponds in a similar way with *R. orientalis*, while in the case of the "type undetermined" diseases it is considered that the type or types of *Proteus* X whose 'O' antigens would correspond with the rickettsiae of these diseases are as yet undiscovered.

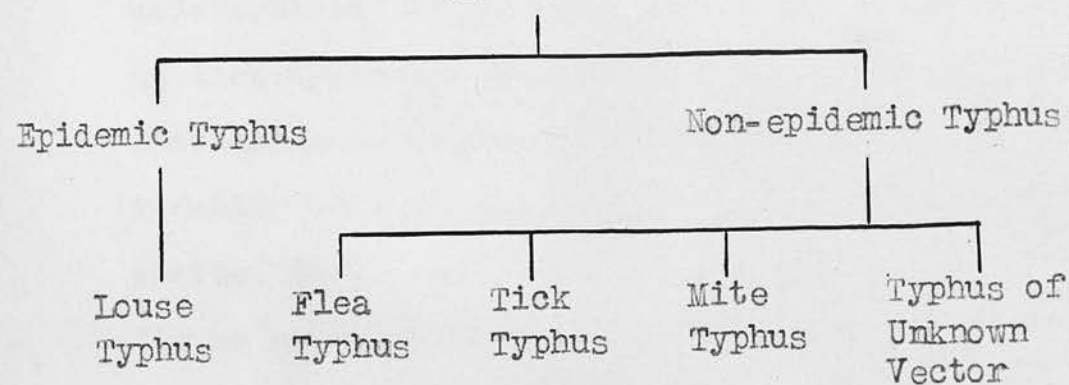
Table 3

Provisional Classification of the Typhus Group of Fevers
after Felix (1935).

Immunological subgroup	Type OX19	Type OXK	Type undetermined
Name of disease	<p>Classical epidemic typhus</p> <p>Tabardillo (Mexico)</p> <p>Brill's disease (U. S. A.)</p> <p>Endemic typhus of U. S. A. and Australia, Greece, Syria, Manchuria, Malay (shop typhus), India, Burma, Phillipines, Hawaii, Toulon (fièvre nautique), etc.</p>	<p>Tsutsugamushi fever of Japan, Formosa, Malay, and Dutch East Indies</p> <p>Scrub typhus of Malay, Dutch East Indies, India, French Indo-China, Australia</p>	<p>Spotted fever of Rocky Mountains</p> <p>Spotted fever of Eastern U. S. A.</p> <p>Sao Paulo typhus</p> <p>Fievre boutonneuse (Mediterranean)</p> <p>Febbre errutiva (Italy)</p> <p>Tick-bite fever of S. Africa</p> <p>Epidemic and endemic typhus of S. Africa</p> <p>Tick-borne typhus of India, Kenya, etc.</p>
Vector	Lice and rat fleas	Mites	Ticks, lice, and rat fleas
Reservoir of virus	Rats. Man	Field mice and rats	Rodents, Dogs, ? Ticks. Man
Agglutination	OX19 + + + OX2 + OXK -	OX19 - OX2 - OXK + + +	OX19 + OX2 + OXK +

Table 2

Typhus Fevers



The agglutination in low or moderate titre only of the three known strains of *Proteus* X in the case of these diseases is in the nature of a group reaction, due to a degree of antigenic relationship between these strains and the as yet undiscovered "main" strain or strains.

Valuable though the classifications just described may be with regard to certain aspects of the diseases of the group, neither of them provides us with a complete statement of the facts as they are at present known. Thus neither of these schemes brings out the interrelationships of the diseases grouped as "type undetermined" in the one, and which would be classified as tick typhus in the other. We know, for instance, that cross-immunity and other tests show immunological identity between Sao Paulo typhus and Rocky Mountain spotted fever, while between the latter disease and fievre boutonneuse there is only partial correspondence. Again, in Felix's classification louse typhus and flea typhus are placed in the same group, though cross-immunity and rickettsial agglutination tests show that though these diseases are immunologically related, differences do exist between them. On the other hand, Megaw's classification places these two diseases in different groups, giving no indication at all of this same relationship.

Which of these two classifications, then, is the better? Admitting that both are incomplete and provisional only, which is the more capable of expansion to admit new facts, and thus give a more complete representation of the position? In the present writer's view, neither classification by insect vector

nor classification by the Weil-Felix reaction are likely to be susceptible of further expansion. On the one hand, it is difficult to envisage any advances in respect of the Weil-Felix reaction: to elucidate the problem of the "type undetermined" diseases on these lines, new types of Proteus X would have to be discovered. Since the first description of the reaction new Proteus X strains have been sought after consistently, but so far have not been found. Also, the serological classification is based on the view that the Weil-Felix reaction is specific, a view which is not by any means universally held (see also Section V).

On the other hand, the classification by vectors obviously leaves no scope for the further subdivision of groups of diseases for which the vector is already known. The only provision is for the addition of new types of vectors.

The more recent use of the rickettsial complement fixation and rickettsial agglutination tests has led to important advances in our knowledge in the relationships between the various members of the typhus group of diseases. Though Ricketts (1909) demonstrated the agglutination of rickettsia bodies by the serum of men and animals recovered from Rocky Mountain spotted fever, this reaction has not been widely used until quite recently, owing to the difficulty hitherto experienced in obtaining suspensions of these organisms. Recent advances in the technique of growing rickettsiae in tissue culture, and more especially in the cultivation of these organisms in the yolk sac of the developing chick embryo and in the

lungs of certain rodents, have enabled us to obtain suspensions of rickettsiae in quantity. Applying the rickettsial agglutination test, Van Rooyen and Bearcroft (1943) showed that the serum of patients suffering from flea borne typhus agglutinates suspensions of the corresponding rickettsiae in higher dilutions than it does suspensions of louse borne typhus rickettsiae. In the same way, the serum of louse borne typhus patients agglutinates the homologous organism in higher dilutions than it does the heterologous. These two diseases cannot be differentiated by the Weil-Felix reaction, the serum from both types of case often giving equally high or low titres with suspensions of *Proteus* OX19. The relationship between *fievre boutonneuse* and Rocky Mountain spotted fever which has already been mentioned further illustrates the point. Plotz et al. (1944) have shown that these two diseases can be differentiated by means of a rickettsial complement fixation test when specific rickettsial antigens are employed, though the Weil-Felix reaction would not permit such a differentiation.

In the same way, it seems probable that tests on similar lines with the other diseases of the group will yield important information. We have, in the rickettsial serological tests, methods whereby we can obtain a direct measure of the antibody response to rickettsial infection. This in turn is a reflection of the antigenic constitution of the causal rickettsia bodies. If, as seems not improbable, we can evolve a classification of the typhus group of diseases based on the antigenic structure of the various causal

rickettsiae, such a classification would truly rest on an etiological foundation.

It must not be considered, from a perusal of the foregoing paragraphs, that the author advocates complete disregard of the earlier classifications. As Cheate points out, classifications are not knowledge themselves, but facilitate the exposition of knowledge. Thus we do in fact require both the serological classification and the classification according to vectors in order to comprehend these aspects of the diseases of the typhus group. The classification based on the antigenic structure of the rickettsiae will, when it comes, probably provide us with a better scheme for the exposition of knowledge, but by itself it will not replace knowledge that has already been accumulated.

For the purposes of this thesis it is considered that classification according to insect vectors is the more useful, and is accordingly adhered to. When the term "typhus fever" is used without further qualification, it is to be taken as ^{con}noting louse borne typhus.

SECTION 11

THE GEOGRAPHICAL DISTRIBUTION OF MITE BORNE

TYPHUS

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Japan; Formosa; Pescadores Islands.

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Malaya: scrub typhus and shop typhus;

Sumatra: "pseudo-typhoid", Sumatran

mite fever, scrub typhus; Java;

Borneo; Phillipine Islands.

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typhus.

New Guinea..... 25

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India: "tick typhus", mite borne typhus;

Ceylon: previous reports of typhus-like

diseases, Western medicine and the

Ayurvedic system, Mite borne typhus;

Burma; Indo-China.

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THE GEOGRAPHICAL DISTRIBUTION OF MITE BORNETYPHUSJapan and Neighbouring IslandsJapan

Towards the end of the last century systematic study was directed towards an endemic disease affecting field workers in certain areas in Japan. This disease, which took the form of a fever of some two to three weeks duration, during the course of which an exanthem resembling that of typhus fever appeared, was known traditionally as the tsutsugamushi disease, and was thought by some to be a local form of typhus fever.

The first systematic description of the condition was published by Palm (1878), though its existence had been recognised for a very long time - for hundreds of years, apparently, according to old records. Baelz (1879) considered that the disease was distinct from typhus fever, and named it Japanese flood fever.

The condition was of a seasonal nature and occurred in certain limited areas. Persons who contracted the disease were found to have frequented the banks of rivers and small islands subjected to inundation, the areas most associated with infection being waste land covered with undergrowth and weeds. The disease occurred only on the west side of the northern part of

the main island of Japan, in the Niigata, Akita and Yamagata prefectures, being localised to the flood basins of the larger rivers, especially the Omanogawa and the Shinanogawa. It occurred only in the summer months, particularly in July and August, when the hemp crop was harvested after the floods.

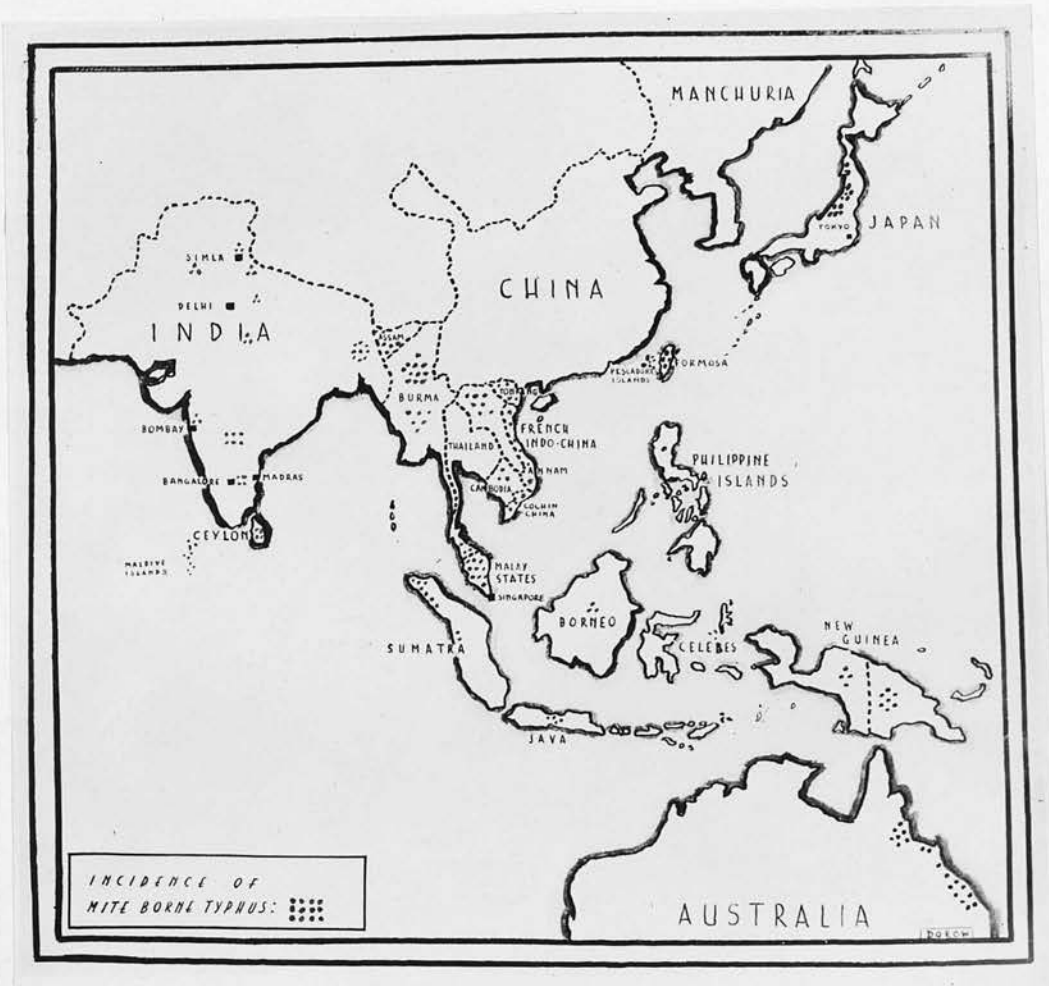


Fig. 1 - Showing the geographical distribution of mite borne typhus.

Investigations into the etiology of the condition brought forward evidence to indicate, as the vector of the disease, a trombidid mite. Later, it was shown that the serum of patients suffering from the disease contained agglutinins for *Proteus* OXK, and with the demonstration of rickettsia bodies as the causal agent, the view that the tsutsugamushi disease was, in fact, of the typhus type became substantiated.

Formosa

Hatori (1919) reported the occurrence of the tsutsugamushi disease in Formosa, where the condition had been observed since 1904. Morashita (1939) reports 166 cases between 1933 and 1938, the population of the island being 5,200,000. The endemic areas appear to be more widely spread than is the case in Japan, the disease occurring not only near river banks but also in cultivated fields, foot hills, and in jungles in the plains and in the mountains. The condition occurs throughout the year, but mainly from May to December and especially from July to October.

Pescadores Islands

These are a group of islands situated in the Formosa strait. The natives had apparently been familiar for some time with an endemic exanthematous disease, from cases of which Naritomi (1933) isolated a rickettsial strain. He showed by cross-immunity tests that this strain was identical with rickettsial strains isolated from cases of the tsutsugamushi disease in Japan. The clinical picture was also found to be similar to that of the Japanese disease, though the mortality rate was much lower (Kawamura and Yamamiya, 1939).

The distribution of endemic areas differs from what occurs in Japan and Formosa. In the Pescadores the endemic areas surround the houses of the islanders and the disease is not known to be contracted in the fields and other localities far from human dwellings. The possible explanation is that the monsoon carries salt water which damages plants and grasses, and so

produces unfavourable conditions for the trombidid mite which is the vector of infection. On the other hand, the ground around the houses is protected by coral walls, and here the mite finds suitable living conditions (Morashita, 1942). The season is from April to November only, with a peak in June and July.

The Malay Archipelago

Malaya

Dowden (1915) reported a case of fever of obscure nature, which seemed to resemble in many respects the tsutsugamushi disease. Apart from this one report however, no further cases were noted till 1924, when Fletcher and Lesslar (1925, 1926) reported the occurrence in Malaya of diseases of a typhus-like nature.

These typhus-like diseases did not represent a single entity: two distinct types occurred, and, later, cases exactly resembling the tsutsugamushi disease of Japan were also noted.

One type of typhus-like disease occurred in towns and villages, and was called urban or shop typhus. This type was associated with the formation of agglutinins in the patients' serum for Proteus OX19. The vector of the disease was found to be the rat flea, and the natural reservoir the house rat.

The other type of typhus-like disease occurred, not in the vicinity of human habitations, but in oil-palm estates and "scrub country". This was rural or scrub typhus, and was thought to be transmitted to man, possibly, by the bite of a larval tick.

In addition, a disease clinically identical with

the tsutsugamushi disease occurred in the same areas as did scrub typhus. This disease was similar in all respects to scrub typhus, except for the fact that an eschar, or primary lesion resulting from the bite of the transmitting arthropod, was never found in cases of the latter disease but was invariably present in cases of the tsutsugamushi-like condition. The serum from cases of both these conditions did not agglutinate suspensions of *Proteus* X19. Instead, antibodies were formed for a variant of this organism, *Proteus* XK. It was considered, also, that in scrub typhus higher titres were obtained in this agglutination reaction than was the case in the tsutsugamushi disease (Fletcher, Lesslar and Lewthwaite, 1929).

Further investigation has simplified the position. Lewthwaite and Savor (1936 a,b,c) isolated rickettsial strains from cases of scrub typhus and the tsutsugamushi disease, and comparison by cross-immunity tests showed the respective viruses to be identical in all respects. The presence or absence of an eschar they showed to be of little significance as a criterion in forming two separate categories of disease (see also Section VII). Further more, the original observations on the respective heights of the agglutination titres in scrub typhus and in the tsutsugamushi disease could not be confirmed. Titres of an equally high, or low, order were found in both types of case. It thus became apparent that no distinction could be held between cases of "scrub typhus" on the one hand, or "tsutsugamushi disease" on the other. Both conditions were, in fact, examples of one and the

same disease entity.

Two types of typhus-like disease therefore occurred in Malaya: urban or shop typhus which corresponded to flea borne typhus in other parts of the world, and rural or scrub typhus or tsutsugamushi disease, which corresponded to the tsutsugamushi disease of Japan and elsewhere. The latter condition occurs in many parts of Malaya. It has been reported from Selangor, Pahang, Perak, Negri-Sembilan, Johore, Kelantan, Trengganu and Kedah (Fletcher and Lesslar, 1925, 1926; Fletcher and Field, 1927; Lewthwaite and Savoor, 1936; Portelly, 1933; Anigstein, 1933; O'Connor, 1935). Beveridge and Underhill (1936) have reported a case from Singapore and Subrahmaniyam (1936) found serological evidence of the presence of the disease in the same city.

The disease occurs, in Malaya, amongst labourers working in areas overgrown with tall grass, and where weeding and pruning are carried out. Those working under trees are especially affected and many cases have occurred among workers on oil-palm estates (Fletcher, Lesslar and Lewthwaite, 1928). O'Connor (1935) observed the disease in cowherds and bullock drivers who had visited overgrown and abandoned agricultural ground. There is no seasonal variation in the incidence of the disease.

Sumatra

Schuffner (1915) published descriptions of a disease which he had noted in Sumatra since 1902, and which he had termed "pseudo-typhoid". He considered the condition analogous to the tsutsugamushi disease

of Japan. Further investigation showed that certain cases occurred, however, which differed from the tsutsugamushi disease, or "Sumatran mite fever" as it was called, in that an eschar was absent. Following the work in Malaya these cases were called "scrub typhus", but again, as in Malaya, the distinction could not, eventually, be upheld.

Wolff (1931) showed that the serum of patients developed agglutinins for *Proteus* XK (and also that there was no difference in the height of the titres obtained in cases of "scrub typhus" and in cases of the "tsutsugamushi disease" respectively), and Kouwenaar and Wolff (1934) isolated the causal rickettsia. This was found to be identical, when compared by cross-immunity tests, with the virus of the Malayan disease (Lewthwaite and Savoor, 1940 a).

The disease occurs on the east coast of Sumatra, and especially at Atjeh, at the Northern extremity. Walch (1923) found the condition to be incident chiefly among workers on tobacco estates situated between the central mountain chain and the east coast. The tobacco fields are cultivated for only one year in every eight or nine. Wolff and Kouwenaar (1936) have also found that the disease occurs in places where uncultivated strips of land have to be cleared. The condition occurs throughout the year.

Java

Wolff and de Graaf (1939 a,b) state that the disease is rare in Java. They isolated rickettsial strains from cases of the disease, and cross-immunity tests showed that these strains were identical with

strains isolated from cases in Malaya. Leimena (1941) also reports a case.

Borneo

The condition has only once been reported from Borneo. The case was typical clinically, and showed a positive agglutination reaction with *Proteus* OXK (Bessem, 1935).

Phillipine Islands

Ashburn and Craig (1908) described a febrile condition observed by them in the Phillipines as being similar to the tsutsugamushi disease. No further accounts, however, have come from these islands.

Australia

Smithson (1910) reported a febrile condition occurring in Queensland, which he termed "Mossman fever", deriving the name from the town where he practised.

Clarke (1913) stated that the earliest white settlers on the Daintree river, north of Mossman, suffered severely from fever, with many fatalities, and that the fever was known among the natives before the arrival of the white settlers in 1877. According to Heaslip (1941), Clarke's description of this fever can be recognised as applying to the tsutsugamushi disease.

Cilento (1923) pointed out the similarity between certain of the Queensland fevers and "Japanese river fever", but a definite diagnosis was not made till 1927 or later by Paine and Nye, according to Langan and Mathew (1935). Unwin (1935) reported on

a series of 1,500 cases of "coastal fever" in Queensland, the condition apparently being identical with the tsutsugamushi disease. This author, and Langan and Mathew (1935) noted that the serum of such cases agglutinates suspensions of *Proteus* OXK.

Cases have been reported from West Cairns, Double Island, Babindo, Tully, Edmonton, Maurylian, El Arish, Jordan Creek, Cairns, Intake, Little Mulgrave, Gordonvale, Queerah, Redlynch, Mossman, Tolga, Daintree, Edgehill, Cooktown, Ingham, Meerawa, Yorkie's Knob, Innisfail, Kuranda, Atherton, Milaa Hilaa, Hambledon. The condition occurs mainly in field workers clearing waste land or scrub country, and cases occur throughout the year (Mathew, 1938).

NEW GUINEA

The first case of typhus-like disease in the mandated territory of New Guinea was reported by Sinclair (1930). Gunter (1935) showed that serum agglutinins developed for *Proteus* OXK in such cases, and that clinically they were similar to the tsutsugamushi disease of Japan and elsewhere. The disease occurs in the Morobe, New Britain, Madang and Sepik districts (Gunter, 1937, 1938, 1940). A series of cases is also reported by van der Borch (1937). One case, confirmed serologically, has been reported from Papua (May, 1941). The disease has also been met with in New Guinea during the present war (Bulletin of the United States Army Medical Department, 1944).

Continental AsiaIndia

Typhus fever has been known in India since the latter part of the nineteenth century (Covell, 1936 a), and cases have been reported from time to time. The first report of a typhus-like disease, however, was given by Megaw (1917). The patient was the author himself, and he considered that the disease had been contracted while on an expedition in the Himalayan forests. He also thought that the disease almost certainly resulted from a tick bite.

Megaw (1921, 1924, 1925, 1928) and his colleagues in a series of papers discussed the etiology of this typhus-like disease, reports of which were now becoming numerous. They summed up the available evidence and decided in favour of a tick as the vector.

As a result of this, most cases of typhus-like disease reported from India have, until very recently, been labelled "Indian tick typhus" as a matter of course. It is important to realise, however, that ticks have never been proved to transmit typhus-like diseases in India, and it is now known that more than one variety of typhus-like fever occurs in that country.

At the same time, the cases reported by Megaw do resemble most closely, of the various fevers of the typhus group, the Rocky Mountain type. This applies also to the reports of some other workers, but a study of the Indian literature leaves one in doubt as to the actual nature of many of the cases reported.

Since the Weil-Felix reaction has come into more

general use in India, and more especially since suspensions of *Proteus* OXK have been available, much light has been thrown on the problem.

The first cases of typhus-like fevers giving agglutination with *Proteus* OXK were reported from Bangalore by Biggam (1932). The next series of cases in which definite agglutination results had been obtained were observed by MacNamara (1935) at Sabathu, Dagshai and Kasauli in the Simla hills, the incidence of the disease being in the summer months, towards the end of the rainy season. As a result of the issue of suspensions of *Proteus* OXK to military laboratories, Boyd (1935) was able to analyse the serological findings in 110 cases of typhus-like fevers, observed over a wide area in India. He found that the cases fell into three groups, according as agglutinins preponderated for *Proteus* OX19, OX2 or OXK. These groups were:-

1. The XK group, in which there were practically no agglutinins for *Proteus* OX19 or for *Proteus* OX2. This group corresponded clinically and serologically to Malayan scrub typhus.
2. The X2 group. This group resembled Rocky Mountain spotted fever.
3. The X19 group, corresponding to endemic (i.e. flea borne) typhus.

Cases of the XK group were reported from Lahore, Bengal and Assam, Meerut, Decan and Burma.

Further cases have been reported from the Simla hills (Bush, 1936). In 1936, out of 4,381 sera examined at the King Institute, Guindy, in Madras Presidency, 16 showed agglutination with *Proteus* OXK in

dilutions of 1 in 200 or higher (Report of the King Institute of Preventive Medicine, 1937). Woodhead and Dutta (1941) have reported cases from Assam. Patel (1943) reported a case of typhus-like disease from Bombay, which gave agglutination with *Proteus* OXK, and Bardhan (1944) has recorded cases from Garhwal (United Provinces) and Jahnsi.

Ceylon

That diseases of the typhus group occur in Ceylon has been known since 1938.

The first cases were recorded by Fernando (1938). These were of the flea borne type, a strain of *rickettsiae* being isolated from rat fleas caught in the house of one of the patients (Wolff, 1939). Two cases of the mite borne type were reported from Colombo by Wijerama (1939), and a further case was recorded by Nicholls (1940). *Rickettsiae* were seen in the peritoneal fluid of a guineapig inoculated with blood from one of Wijerama's cases.

Despite the fact that only three cases of the mite borne type of typhus have been reported from Ceylon, it is now known that cases of this disease, and of the flea borne type also, occur not infrequently. The reasons for this paucity of recorded cases may be mentioned: some of them apply equally to other countries in the East.

There are two systems of medicine in Ceylon: Western Medicine and the indigenous Ayurvedic system. The practitioners of the Western system are mostly employed by the Government. This ensures to some extent that the facilities of modern medicine are avail-

able to the rural population, since the smaller number of private practitioners have always tended to concentrate in the larger towns.

The practitioners of the Ayurvedic system are also to be found throughout the country, and they enjoy considerable popularity, especially with the rural population and the poorer classes. In this way, a large section of the population receives its medical attention from practitioners of a system which does not avail itself of the diagnostic methods of modern medicine.

At the same time, awareness of the presence of typhus-like diseases has not been uppermost in the minds of the practitioners of the Western system, in a country where the commonest cause of pyrexia is malaria, and where typhoid is endemic. It is safe to state that the vast majority of cases of pyrexia receive quinine, at the beginning of the illness at any rate, whether or not malaria parasites have been demonstrated in the blood. Should the temperature remain elevated the diagnosis is reconsidered, and since the typhus-like diseases bear a superficial resemblance to typhoid, it seems not unlikely that many cases have thus been diagnosed.

Since the arrival of military forces in Ceylon, cases of the mite borne type of typhus have occurred from time to time. A fairly large number of cases occurred at the end of 1943. The known endemic areas are in the low country, and are mainly "chena" clearings. These are strips of jungle which are cleared, cultivated intensively so long as the yield of crops

remains good, and are then abandoned. The derelict clearings thus become overgrown with weeds and scrub, forming ideal foraging sites for rats. This is especially the case since quantities of grain are left lying on the ground.

Burma

Kundu (1932) described the first case of a typhus-like fever occurring in Burma. The serum from this case agglutinated suspensions of *Proteus* OX19. Martin and Armstrong (1933) reported the first case in which there was agglutination of *Proteus* OXK. Clinically, the disease resembled mite borne typhus. Maitra and Sen Gupta (1936) showed that this type of typhus-like disease was distributed over a wide area in Burma. They received sera giving a positive agglutination reaction from Rangoon, Syriam, Henzada, Prome, Toungoo, and Bassein in lower Burma, and from Yametha, Meiktila, Kyauksi, Shiwebo, Chin hills, Katha, Southern Shan States, Northern Shan States, Mandalay, Maymyo, and Miyitkina in upper Burma.

Indo-China

The distribution of mite borne typhus in the French possessions in the East is wide.

The first case was reported by Lagrange (1923), from Annam. In Cochin-China the first case was reported by Souhard (1923) and his co-workers, and Ragiot and Delbove (1934, 1935) isolated from patients a rickettsial strain which gave the characteristics of a tsutsugamushi virus. Cases have also been recorded from Cambodia (Delbove et al., 1938), Hanoi (Bruneau and Chapuis, 1938) and Indo-China (Souhard and

Tournier, 1937).

Conclusions

The mite borne type of typhus is a disease already known to be widely distributed over India, South East Asia, the Malay Archipelago, Japan and Australia. It is highly probable that our knowledge of its incidence will be considerably widened when further reports are published after the war.

The endemic areas of the disease form a continuous land mass from India to Indo-China, and an island chain from the Malay Archipelago to the islands of Japan, extending between the latitudes of 40 deg. N. and 30 deg. S. In the continental distribution of the disease, it is surprising to find its apparent absence from China; and there are no reports of the presence of the condition in Siam.

In the case of China, other diseases of the typhus group have been found to occur in that country, and active investigation has been going on for some time. It does not seem likely, therefore, that cases in any number could have occurred without detection. In fact, tentative suggestions as to the existence of a tsutsugamushi-like disease in China have been put forward, but would appear to be of little significance. (Faust, 1923; Raynal, 1939). Statements that the disease existed in China in ancient times are found in some of the Japanese reports (Kitashima and Miyajima, 1918). It is interesting to note that no Chinese trombididae have been described.

The disease has not been reported from the coast-

al areas north of China - Manchuria and Korea - though Weir (1915) met with a condition he described as "paratyphus" in Korea. The exact nature of this disease remains uncertain. It seems unlikely, here too, that the condition can have been overlooked by the temporary occupants of these areas, familiar as they are with the manifestations of the disease.

In the case of Siam, the possibility of the condition being incident in that country would appear to be more likely, bounded as it is by Burma to the West and Indo-China to the North, South and East. It is to be noted, however, that the areas in which mite borne typhus occurs are often very sharply localised, and that the disease should not occur in a country bordered on all sides by territories in which the condition is well known is not by any means impossible.

Concerning the incidence of the disease in the islands of the Malay Archipelago and the South West Pacific area, we are on less sure ground. Those areas from which the disease has not been reported are the islands which have been least subjected to penetration by representatives of the civilised nations, and what practitioners of the Western system of medicine there may happen to be in these territories have little or no access to modern diagnostic facilities.

The present conflict, however, is leading the combatants into areas previously but little known to outsiders. Already reports are to hand of the occurrence of the disease in the "South Pacific area" (Park and Offenkrantz, 1943; Ahlm and Lipschutz, 1944). and the conclusion of hostilities will probably bring us

further accounts.

Discussion of seasonal variations in the incidence of the disease will be deferred till Section IV.

SECTION 111

ETIOLOGY: RICKETTSIA ORIENTALIS

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ETIOLOGY: RICKETTSIA ORIENTALISIntroductoryThe rickettsia bodies

The rickettsioses - those diseases which are caused by rickettsia bodies - include, as well as certain other diseases of man and some diseases of animals, the typhus group of fevers.

The rickettsiae are minute cocco-bacillary bodies measuring less than 1μ in length, though larger and pleomorphic forms are also found. They are non-motile and are Gram-negative. Staining is poor with aniline dyes used in the ordinary manner, though if freshly prepared buffered solutions, such as those of Machiavelli or Castaneda be used, good results may be obtained. Prolonged staining with weak Giemsa's fluid gives the best results.

The rickettsiae, are, primarily, parasites of insects, and man becomes infected by contact with certain blood-sucking arthropoda. In addition, however, to occurring in the lice, fleas, ticks and mites which may parasitise man and give rise to disease, rickettsiae, or bodies very similar to them, are widely distributed in other arthropoda, occurring in the gut contents and lining cells of the alimentary canal and elsewhere. Hertig and Wolbach (1924) listed 45 species of rickettsiae occurring in different insects, most of which were blood-suckers or fed on

animal tissues. Some rickettsia-infected insects, however, were not parasitic. Again, of the blood-sucking insects, some were not known to transmit any disease to man, for instance the bed-bug (*Cimex lectularius*), which is constantly infected with rickettsiae (*R.lectularii*).

Whether or not these rickettsia-like bodies, either those which exist in blood-sucking arthropods but are non-pathogenic, or those which are found in non-parasitic insects, should be classed as Rickettsiae, has given rise to some discussion. Arkwright (1930) states that it seems doubtful whether the various species of rickettsiae described are nearly related. Their resemblance might be partly due to their parasitism of the invertebrate hosts. It seems best, he concludes, to restrict the name "Rickettsia" to those organisms which consist chiefly of very minute forms found in the intestines of a blood-sucking arthropod, there being good reason to suppose that the rickettsia is derived from the host's blood. The name should only be further extended to similar microbes when the resemblance to a well-characterised species is very close.

There is much doubt as to the essential nature of the rickettsia bodies. Pinkerton (1942) states that the rickettsiae are strictly dependent on intracellular conditions, as are the smaller viruses, but the rickettsiae have a somewhat more complex enzyme system and are therefore able to maintain a certain amount of independent metabolic activity within their host cells. From the point of view of size and of

independent metabolic activity, they may be regarded as midway between certain cytotropic bacteria and the viruses. The rickettsiae, however, are not filterable except for *R. diaporica*, the causal organism of Q fever. The pathogenic rickettsiae cannot be cultivated on artificial media, though if living cells be added, a growth may be obtained. Like the viruses, also, the rickettsiae grow well on the chorio-allantoic membrane of the developing chick embryo, and especially well in the yolk sac.

Antigenic structure of the rickettsiae

Most of the work carried out on this subject deals with *R. prowazeki*, and no reports on the detailed antigenic analysis of *R. orientalis* are available. The results of research on the former organism, however, are of present interest since it would seem likely that examination of *R. orientalis* will yield results of a comparable order.

R. prowazeki possesses at least two antigenic components. One of these is heat-labile and the other is heat-stable (Castaneda and Zia, 1933). The heat-stable component is also alkali-stable (White, 1933), and according to Felix (1942) citing Weil and Felix (1921), it is this fraction of the antigenic complex of *R. prowazeki* which is common to that organism and *Proteus* OX19.

The question of the part played in immunity to typhus fever by these antigenic components of *R. prowazeki* is not completely understood. Immunity to this organism cannot be produced in susceptible animals by injection of *Proteus* OX19, even though antibodies to

Proteus in high titre may result. That is to say, immunity to infection does not depend alone on the production of antibodies to the heat-stable antigenic fraction of *R. prowazeki*, which corresponds to the 'O' antigen of *Proteus* X19. Castaneda (1934, 1935, 1936a b, c) has shown that *Proteus* OX19 immune serum reacts with rickettsiae in agglutination, precipitation and complement fixation, though not in opsonisation. But opsonins can be demonstrated in the serum of animals inoculated with *R. prowazeki*. Therefore the heat-labile antigenic component of *R. prowazeki* is that which stimulates production of opsonins.

Felix (1942) suggests that the two antigenic components of *R. prowazeki* can be considered as analogous to the 'Vi' and 'O' antigens of *Bact. typhosum*. The heat-stable component corresponds to the 'O' antigen in that it cannot alone stimulate immunity, while the heat-labile component corresponds to the 'Vi' antigen in that it stimulates the production of opsonins and prevents the interaction of 'O' antigen and 'O' antibody. Felix assumes that the heat-stable component of *R. prowazeki* is an endotoxin, as are the 'O' antigens of the organisms of the *Salmonella* group. He supports this view by quoting the experiments of Friedberger and van der Reis (1919) and Fleck (1931). Intradermal injection of heat-killed suspensions of *Proteus* OX19, or extracts of this organism, produces a local inflammatory reaction. In typhus fever patients, however, the reaction is negative after the fifth or sixth day, remaining so throughout convalescence and sometimes up to several months after recovery.

This period coincides with the presence of serum agglutinins for *Proteus* OX19 in significant titre. In this way the toxicity to man of the OX19 antigen, and its specific neutralisation, are demonstrated.

Felix suggests that the not entirely satisfactory results attending the use of rickettsial vaccines may be due to the likelihood of the method of preparation of these vaccines destroying the heat-labile antigenic factor. If a vaccine containing the full antigenic complement of the rickettsiae could be obtained, it would probably be more efficient than those in present use. In the same way, therapeutic antisera should contain antibodies to both the antigenic components of the rickettsiae. Results are awaited.

Rickettsia orientalis

In section 1 the discovery of the causal organism of typhus fever was mentioned. It was not till a number of years later that the cause of the tsutsugamushi disease of Japan was also demonstrated to be of a rickettsial nature. Early work on the subject brought forth a number of hypotheses, analogous to those which had been advanced in the case of typhus fever, but which have since been disproved.

Nagayo et al. (1917) thought the cause of the disease to be piroplasm-like organisms found in the spleen and other organs. Ogata (1917) incriminated a filamentous fungus which could be cultivated on artificial media. Hayashi (1920) described an organism found in leucocytes and tissue cells in spheroid and ring-shaped forms, which he considered allied to

Theileria parva (of African cattle fever). He named this organism *Theileria tsutsugamushi*, and later claimed priority in describing the causal rickettsia of the disease, *R. tsutsugamushi*. His description and figures are not very convincing (Hayashi, 1932). Sellards (1923) thought the disease to be caused by *Rickettsia nipponica*, an organism he had cultivated on chocolate agar.

The first definite demonstration of the rickettsial origin of the condition was given by Nagayo (1930) and his colleagues. They showed that injection of the blood of a patient suffering from the tsutsugamushi disease into the anterior chamber of a rabbit's eye causes a specific iridocyclitis. The incubation period varies from 4 to 15 days, and in the first few days after injection a non-specific inflammatory reaction may occur. This is transitory. The specific reaction commences as a circumcorneal injection and is followed by turbidity of the aqueous humour. Recession of the inflammation takes place after 7 to 10 days, with the commencement of pannus formation. By withdrawal of aqueous humour from the eye of a reacting rabbit and injection of this into the eye of a fresh animal, the specific iridocyclitis can be transmitted in series indefinitely. These workers showed that in films made from scrapings of Descemet's membrane numerous rickettsia bodies were present in the lining endothelial cells. These they named *R. orientalis*.

Morphology

R. orientalis, as seen in preparations from

Descemet's membrane of the rabbit's eye, or in peritoneal films from infected white mice, is a rod-shaped, bacilliform structure, $0.8-2\mu \times 0.3-0.5\mu$. It stains well with a variety of reagents. With Giemsa's stain it appears as a short rod with two deeper staining polar granules and a paler connecting portion (Fig. 2). The organism stains well by Leishman's method and good results are also obtained with Fielding's (1943) modification of Breinl's method. Methylene blue alone gives adequate results. Machiavelli's and Castaneda's methods do not act well with *R. orientalis*.

The rickettsiae are always found intracellularly within the cytoplasm, but not invading the nucleus, except for those free-lying organisms which have escaped from ruptured cells. The organisms tend to form small groups lying close to the nucleus.

R. orientalis differs from *R. prowazeki* in certain respects. It stains well by Leishman's method, which the latter organism does not. The linear and filamentous forms often exhibited by *R. prowazeki* are not seen in the case of *R. orientalis*. *R. orientalis* is also generally rather thicker and more compact in appearance than is *R. prowazeki*.

Resistance of *R. orientalis*

Kawamura et al. (1915) found that the pathogenicity of citrated blood containing the virus of the tsutsugamushi disease was destroyed by exposure to a temperature of 37 deg. C. for one week, and by keeping the blood in the ice-chest for 10 days. Nagayo (1923) found the virus to be inactivated by 5 minutes exposure to a temperature of 50 deg. C. though not by 30

minutes exposure to 45 deg. C. In infected spleen, rapidly dried in vacuo and stored at 2 deg. C., pathogenicity was unimpaired after 3 days but abolished after 8 days.



Fig.2. -Smear preparation from peritoneum of mouse, showing intracellular *R.orientalis*

Distribution of *R. orientalis* in the tissues

The rickettsiae have been shown by animal inoculation to be present in the blood, lymph glands, bone marrow and spleen of cases of the disease (Nagayo, 1923), and by direct histological demonstration Lewthwaite (1936) has shown their presence in the endothelial cells of the cerebral capillaries.

Kawamura et al. (1915) showed that the blood and lymph glands are infective for animals during the incubation period. The blood ceases to be infective with defervescence though the spleen may retain its infectivity three weeks after the cessation of fever. The virus could not be detected in the cerebrospinal fluid, urine, or in foetal umbilical blood. It does not pass through Berkfeld N or V filters.

Isolation of Strains of R. orientalis

Isolation of *R. orientalis* from cases of the disease provides absolute proof of the nature of the condition, a positive Weil-Felix reaction being presumptive evidence only.

Generally, however, it is not necessary to isolate the causal organism from the diagnostic point of view alone. The diagnosis of the disease can often be made from the clinical manifestations alone, or with the added, though often delayed assistance of the Weil-Felix reaction. This is especially the case when the patient comes from a known endemic area. On the other hand, sporadic cases, especially when clinically atypical and occurring in areas from which the disease has not previously been reported, may present a more difficult problem. In such cases efforts should be made to isolate the causal rickettsiae.

In addition, it is necessary to isolate strains of rickettsiae in order to compare them with strains already isolated elsewhere, to provide material for rickettsial serological tests and for the production of vaccines, and for scientific study generally.

Strains of *R. orientalis* are isolated by inoculating susceptible animals with infected material. When obtained from patients suffering from the disease the material usually consists of blood. The blood is injected directly, or it is allowed to clot, the serum removed and the clot ground up in saline and injected. This method was suggested by Giroud (1935) for the isolation of *R. prowazeki* from patients in a rather late stage of the disease. Removal of the serum is

thought to favour infection of the injected animal by ensuring that virus only, and no serum immune bodies which have developed during the course of the disease, are injected. Infection of experimental animals can also be secured by the injection of red cells removed from citrated blood. Suspensions of internal organs obtained at autopsy have also been used.

Guineapigs

Though these animals have been used in the past more than any other experimental animals in work with *R. orientalis*, they are, for the purpose of isolating strains, perhaps the least suitable. The virulence of different strains of *R. orientalis* for guineapigs varies considerably, in most cases being of a low degree.

In Malaya, Lewthwaite and Savoor (1936 a) inoculated a large number of guineapigs with blood and other material from cases of mite borne typhus before they were able to establish a strain which could be transmitted indefinitely in these animals. They finally succeeded by employing guineapigs fed on a vitamin deficient diet, a method which had been found of value in securing infection in the case of *R. prowazeki* (Zinsser et al., 1931). They also note that previous workers in Malaya had attempted, without success, to isolate strains, though in some instances the guineapigs showed febrile reactions.

Covell (1936 b) found the same difficulty in India. He was unable to isolate a strain of rickettsiae, though some guineapigs reacted with fever.

On the other hand, Kouwenaar and Wolff (1934)

found that the virus of "Sumatran mite fever" produces a severe illness in guineapigs, with a mortality rate of 63%. These workers also note that in Japan guineapigs have been found to react poorly to infection.

The present writer carried out the following experiments with cases of the mite borne type of typhus in Ceylon. Three series of guineapigs were used. In the first series, 10 animals were inoculated with blood from 12 patients. The day of disease varied between the 7th. and the 14th. The inoculum of 5 cc. volume consisted of the clot from 5 cc. whole blood ground up in sterile normal saline, and was given intraperitoneally. In the case of two guineapigs the inoculum consisted of pooled clot suspension from two patients. The animals' rectal temperatures were taken twice daily, and in all cases where passage was not made, the animals were observed for 30 days. None of the animals reacted with pyrexia, nor was a scrotal reaction observed. One guineapig from this series was killed on the 8th. day after inoculation, and suspensions of the brain and spleen were pooled and injected intraperitoneally into another animal. This second guineapig was killed 21 days later, and two subsequent passages were made at 12 day intervals. No reaction was obtained in any of the animals, nor were rickettsiae seen in smears from the tunica vaginalis or peritoneum.

A second series of guineapigs were inoculated with autopsy and biopsy material. One animal was inoculated with 5 cc. of a suspension of brain from a fatal case, but died the following day from bacterial

infection. Two animals were inoculated with a suspension of lymph glands removed at autopsy from a patient who had died on the 18th. day of the disease. These animals were killed 12 days after inoculation and passages made. No reactions were obtained. One patient developed a splenic abscess on the 30th. day of the disease. This was aspirated on the 37th. day, only blood and splenic tissue being obtained. This material was inoculated intraperitoneally into a guineapig and two subsequent passages were made at 12 day intervals. No reactions were noted.

A third series of guineapigs were inoculated with blood clot suspension from two patients in the 12th. day of the disease. Passages were made every 12 days for 4 generations. This series will be referred to later.

Rabbits

As already mentioned, inoculation of material containing *R. orientalis* into the anterior chamber of the rabbit's eye causes a specific iridocyclitis, and rickettsiae can be demonstrated in the endothelial cells lining Descemet's membrane (Nagayo et al., 1930).

Lewthwaite and Savor (1936 a, b) report considerable success with this method, though they point out that there is difficulty in maintaining the strain through the first three generations. Wolff and Kouwenaar (1935), working with Sumatran cases, reported much less constantly positive results, and obtained only one positive reaction when using patients' blood. Covell (1936 b) also found difficulty in infecting the eye of the rabbit.

In the present author's experiments, 4 rabbits were inoculated in the anterior chamber with blood from 4 cases of the mite borne type of typhus in the 12th. day of the disease. No reactions were obtained. Another rabbit was inoculated with brain suspension from a patient who had died on the 18th. day of the disease. Four rabbits were inoculated with suspensions of lymph glands which had been removed at biopsy for histological examination. No reaction was obtained in any of these animals.

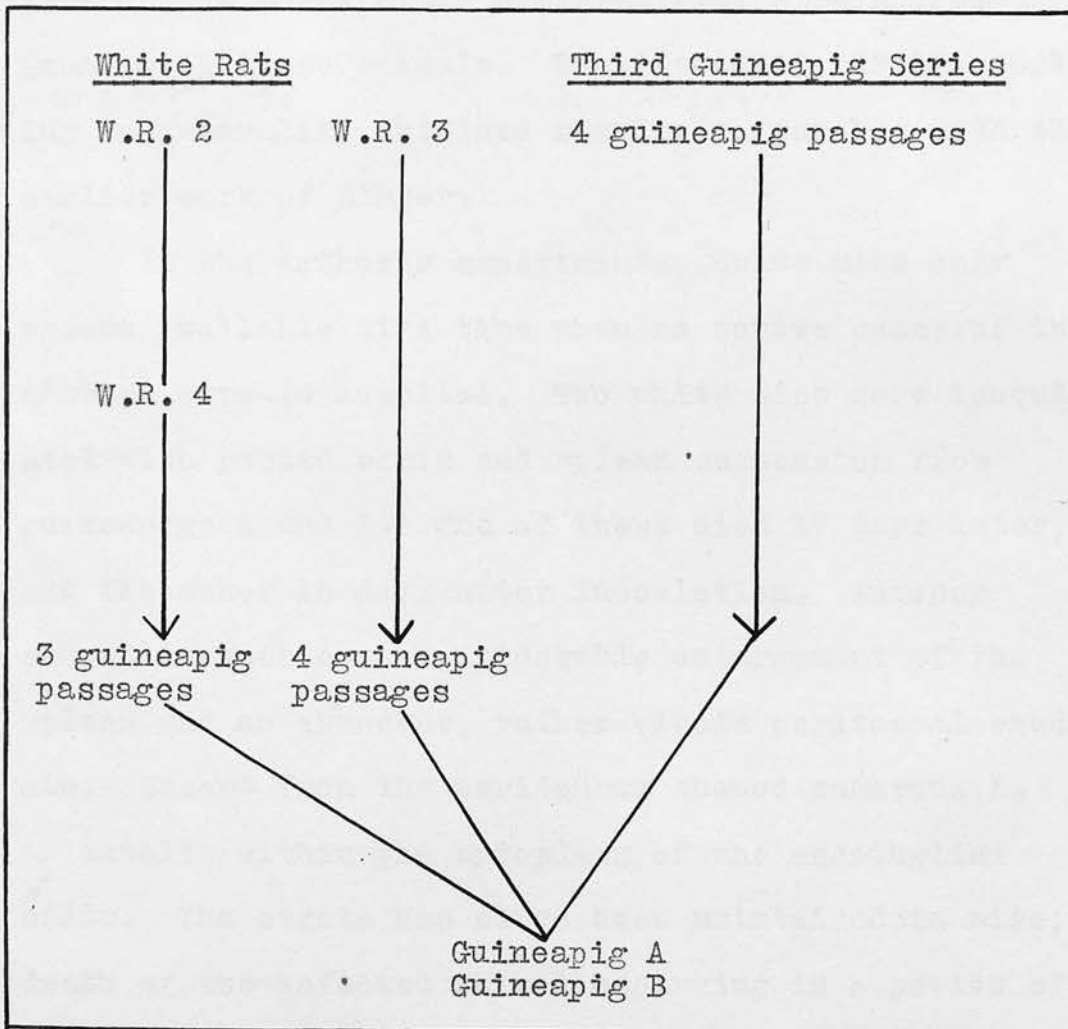
White rats

Lewthwaite and Savoor (1936a, b) were able to infect white rats with *R. orientalis*, and found that the infection could be transmitted in series in these animals indefinitely. Infected rats showed little or no fever, and there was no scrotal reaction. Rickettsiae were found, though in very small numbers, in smears from the tunica vaginalis. Webster (1940), however, states that numerous rickettsiae may be found in such smears.

In the experiments now being described, 3 white rats were inoculated with 4 cc. ground-up blood clot in normal saline from 3 patients in the 14th. day of the disease. The first rat died within 2 hours, the second died on the 19th. day, and the third was killed on the 21st. day, after inoculation. The second rat showed enlargement of the spleen at post-mortem examination, but no abnormalities were found in the third. Rickettsiae were detected in neither rat. Passages were made from these animals, and in addition material from the third guineapig series was also incorporated.

The experiments carried out up to this point are shown in Table 4. All the guineapig passages shown were made at 12 to 14 day intervals. None of the animals developed pyrexia, or showed any other signs of infection, either during life or at post-mortem examination. The last two guineapigs, A and B, were killed 14 days after inoculation, the brains and spleens pooled, and 1 cc. of suspension injected intraperitoneally into each of two white mice.

Table 4



White mice

There are again differences in the experience of various workers concerning the results of infection with *R. orientalis* in white mice. Dinger (1933) found these animals to be very susceptible to infection, as did Wolff and Kouwenaar (1934). Tanaka et al., (1930) on the other hand found them to be resistant to the virus of the tsutsugamushi disease, and according to Heaslip (1941) this has been the experience of most other Japanese workers. Lewthwaite and Savoor (1940) were unable to maintain a rickettsial strain from Sumatra in these animals. Heaslip (1940, 1941), working in Australia, obtained results comparable with the earlier work of Dinger.

In the author's experiments, white mice only became available at a time when no active cases of the disease were in hospital. Two white mice were inoculated with pooled brain and spleen suspension from guineapigs A and B. One of these died 17 days later, and the other 18 days after inoculation. Autopsy showed in each case considerable enlargement of the spleen and an abundant, rather viscid peritoneal exudate. Smears from the peritoneum showed numerous *R. orientalis* within the cytoplasm of the endothelial cells. The strain has since been maintained in mice, death of the infected animal occurring in a period of 15 days on the average, the extremes being 8 to 20 days.

Experiments with the developing chick embryo

Since the rickettsiae of certain other diseases of the typhus group have been shown to grow well in

the yolk sac of the developing chick embryo, an attempt was made to obtain a growth of *R. orientalis* in a similar manner.

Ten fertile hens eggs, incubated for 6 days at 39 deg. C. were inoculated according to Cox's (1938) technique with 0.5 cc. blood clot in saline from 7th. to 12th. day cases. Only three embryos died within 6 days of inoculation, and in these cases bacterial infection was responsible. The remaining embryos continued to develop for some days, but eventually all died. They were found to be bacteriologically sterile. *Rickettsiae* could not be demonstrated.

Comparison of Strains of *R. orientalis*

Strains of *R. orientalis* having been isolated from cases of mite borne typhus in widely separated parts of the world, it has been necessary to compare these strains with each other with regard to their immunological properties.

In the case of the *rickettsiae* of the other members of the disease of the typhus group it has often been possible to perform rickettsial complement fixation and rickettsial agglutination tests as well as to carry out cross-immunity tests. As suspensions of *R. orientalis* in a form suitable for serological reactions have not yet been obtained, only cross-immunity tests with experimental animals have been used for the purpose of comparing strains.

Reaction in animals of strains of *R. orientalis*

1. Cross-immunity tests

For the purpose of cross-immunity tests guinea-

pigs and rabbits are the most suitable animals. Monkeys can also be used.

i. Guineapigs

Guineapigs are employed when the strains of *R. orientalis* to be compared give rise to a febrile reaction in these animals. The method is as follows. A number of guineapigs are inoculated with one strain of *R. orientalis*. The ensuing febrile reaction is noted. A period of recovery of at least six weeks is then allowed. In order to show that immunity to the homologous organism is produced, the animals are re-inoculated with the same strain. There should be no subsequent pyrexia. In the same way, with another series of animals, immunity to the homologous organism is demonstrated in the case of the second strain.

The two strains are now compared with each other. Guineapigs are inoculated with one strain, allowed to recover from the reaction, and are then inoculated with the second strain. If no reaction now results, immunity to the heterologous organism has been produced. In the same way another series of animals are first immunised to the second strain and then tested for heterologous immunity to the first strain. To demonstrate that the two strains are immunologically identical, it is thus seen that in each case immunity to the heterologous organism must be produced.

ii. Rabbits

The principles of cross-immunity testing in rabbits are the same as those which obtain in the case of guineapigs.

The specific iridocyclitis is produced in one eye of the test rabbit by injection into the anterior chamber, of one strain of *R. orientalis*. At least six weeks after subsidence of the reaction is allowed for recovery. Immunity to the homologous organism is then demonstrated by injection of the same strain into the remaining eye. No reaction follows. A similar test is made in the case of the second strain. The two strains are then compared with each other, the first strain being introduced into one eye, and after recovery from the reaction the second strain is injected into the unused eye. As in the case of guinea-pigs immunity to the heterologous organism is shown for each strain.

Instead of using the eye, a local necrotic lesion may be produced by intradermal inoculation of the virus. The resulting immunity prevents the development of another such lesion on injection of an immunologically identical organism.

2. Stimulation of agglutinins.

Inoculation of rabbits with rickettsiae results in the production of agglutinins for that type of *Proteus* OX with which the particular rickettsial strain is associated. Felix (1933) showed that a second injection of the homologous organism does not lead to re-stimulation of the agglutinins. This fact has been used as a method of comparing strains of *R. orientalis*. Lewthwaite and Savor (1936 c) found that only some 50% of rabbits developed agglutinins for *Proteus* OXK when inoculated with *R. orientalis*, but having allowed time for the highest titre of

agglutinins to develop (a matter of some three months), there was no restimulation of agglutinins on further inoculation.

The author has compared the strain of *R.orientalis* he isolated in Ceylon with a strain from Assam, kindly supplied by Dr. S. R. Savoor. Neither strain produced a febrile reaction in guineapigs, and they were therefore compared by intraocular injection in rabbits. The inoculum consisted of a 1 in 10 dilution in sterile normal saline of peritoneal exudate from infected white mice. The interval allowed after the ocular reaction was six to eight weeks. The results of the experiments are given in tabular form (Tables 5 and 6). The strains proved to be immunologically identical.

The results of cross-immunity tests have shown, in all cases where they have been applied, that the strains of *R.orientalis* tested are immunologically identical. There is no cross-immunity between flea borne and mite borne typhus, or between the mite borne type and Rocky Mountain spotted fever.

Conclusions

The diseases of the typhus group are caused by minute bacilliiform bodies, the rickettsiae. As well as causing these, and other, diseases, rickettsiae are found, apparently in a state of symbiosis, in various arthropoda.

Laboratory animals are susceptible to infection with the causal organism of the mite borne type of typhus, *R.orientalis*, the white mouse being extreme-

Table 5

Immunity to the homologous organism

Inoculations					
Ceylon strain			Assam strain		
	1st.	2nd.		1st.	2nd.
Rabbit 1	+	-	Rabbit 5	+	-
" 2	+	-	" 6	+	-
" 3	+	-	" 7	+	-
" 4	+	?	" 8	+	-

The ? against rabbit 4 signifies that there occurred what appeared to be a feeble reaction.

Table 6

Immunity to the heterologous organism

Inoculations					
	Ceylon strain	Assam strain		Assam strain	Ceylon strain
Rabbit 9	-	+	Rabbit 13	-	+
" 10	-	+	" 14	-	+
" 11	*	*	" 15	-	+
" 12	-	+	" 16	-	+

* In rabbit 11 the eye became infected with Staph. aureus. The animal was destroyed.

In both tables the "plus" sign indicates the development of a rickettsial iridocyclitis.

ly so, at all events in the case of certain strains of the virus.

The virulence for guineapigs of this organism however, is often low. It has usually been considered in previous work on the isolation of strains of *R. orientalis*, that guineapigs which fail to react with pyrexia after inoculation with infected material are of no further value in such isolation experiments. Similarly, when passage animals have failed to show a pyrexial reaction after the initial animals in the series had so responded, the strain has been considered as lost.

The author's experiments, however, indicate that though guineapigs may not react obviously to inoculation, yet the rickettsial strain can ultimately be recovered after causing an inapparent transmissible infection. This inapparent infection has been transmitted through at least four generations of guineapigs.

The failure to obtain reactions in rabbits, using patients' blood, may be explained on the grounds of possible differing in virulence of various strains of rickettsiae for these animals, in the same way as they differ for guineapigs. The contrast between the Malayan and the Sumatran reports supports this view. Infection of the rabbit's eye was secured later by inoculation of the peritoneal exudate of infected mice, even in a dilution of 1 in 10. This exudate is extremely potent as an infecting agent; much more so than is the blood of a patient, since it contains large numbers of rickettsiae.

Failure to infect the yolk sac of the developing chick embryo may be explained, possibly, on similar grounds. The concentration of rickettsiae in the blood of patients may be insufficient to secure infection of the yolk sac, whereas the high concentration found in material from passage animals might produce successful results. It is also possible that the chick embryo is an unsuitable medium for the growth of *R. orientalis*. Gispen (1941) has shown that the virus of "scrub typhus" and "Sumatran mite fever" fails to grow on the chick egg membrane, but grows well on the chorio-allantoic membrane of duck eggs. Possibly a similar state of affairs exists with regard to the yolk sacs of these respective species.

Cross-immunity tests have shown that all strains of *R. orientalis* so far compared, are immunologically identical. The author has shown the Ceylon strain to be immunologically identical with a strain from Assam.

SECTION IV

ETIOLOGY: VECTOR AND RESEVOIR

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ETIOLOGY : VECTOR AND RESEVOIRTrombidiid Mites

The tsutsugamushi disease of Japan was traditionally believed by the inhabitants of the endemic areas to be caused by the bite of a minute insect, the akamushi (red bug) or kedani (hairy mite). The name "tsutsugamushi" means "dangerous bug".

Baelz (1879) in one of the earliest systematic studies of the condition described the insect which was thought to cause the condition, and found it to be a larval mite. He thought, however, that it had no etiological connection with the tsutsugamushi disease.

Tanaka (1899) revived the old view, though no immediate proof was offered. Brumpt (1910) gave a definite description of the larval mite and named the species *Trombicula akamushi*, assigning it to the genus *Trombicula* Berlese (1905). Miyajima and Okamura (1917) studied the life cycle of the mite and succeeded in rearing adults in the laboratory for the first time. According to these workers, the larva is hexapod, yellowish-red in colour, and measures 0.32 to 0.43 mm. in length. It remains on the host for three to four days, during which time it feeds and swells. It then drops off and seeks shelter in the ground. In five to six days, in hot weather, metamorphosis to the nymphal stage takes place. The size of the young nymph, which lives on

vegetable juices, being neither parasitic nor predaceous, does not exceed that of the fully fed larva. A further ten weeks is required before the imago, which is similar to the nymph in appearance but many times larger, appears. The adults lay eggs, not in clusters as do the common trombididae, but singly. The larva hatches out in about three weeks.

In nature, the larva is found under dead leaves or on decaying vegetable matter, or attached to its vertebrate host. It feeds only once, after which it drops off the host and metamorphosis commences. The length of the life cycle under natural conditions is not exactly known. It is thought that the mite passes the winter in the adult stage, the mature insects depositing their eggs in the soil late in May. Oviposition may continue till September, while hatching commences in June.

Adults of *T. akamushi* have also been bred out in the laboratory by Nagayo et al. (1917). These workers describe five species of trombidid mites occurring in Japan, but state that only *T. akamushi* attacks man.

Experiments to demonstrate the vectorship of the tsutsugamushi disease by *T. akamushi* have been carried out in Japan. Miyajima and Okamura (1917) obtained larvae from endemic tsutsugamushi areas. They bred these in the laboratory, as described above, and applied 28 larvae of the next generation to a monkey. The mites attached, and in about 7 days time two ulcers developed, one on the chin and one on the left mamma. The temperature became elevated between

the 7th. and 12th. days. The left axillary glands enlarged, and the animal was very ill. Ultimately it recovered. According to Miyajima and Okamura, this work confirms experiments first carried out by Kitashima and Miyajima (1909).

Nagayo (1923) reproduced a pyrexial disease in monkeys by injection of blood from patients suffering from the tsutsugamushi disease. On recovery such monkeys were immune to further injections of patients' blood. Adult mites and nymphs, bred out from larvae collected in areas where the disease was endemic, were ground up and injected into monkeys. A similar condition, with subsequent immunity, was produced.

Animals have also been infected by keeping them in endemic areas, where they have been attacked by larval *T. akamushi*. Monkeys were thus infected (Kitashima and Miyajima, 1918; Hatori, 1919), and guinea-pigs (Hayashi et al., 1933). The last named workers were able to demonstrate rickettsiae in the tissues of the guineapigs.

Kawamura and Imagawa (1931) found masses of rickettsiae in the salivary glands of a larval *T. akamushi* removed from a field mouse trapped in an endemic area.

In Japan, the reservoir of the infection is considered to be the field vole, *Microtus montebelli*. Trapped in endemic areas, these rodents have been found to harbour large numbers of *T. akamushi* larvae. The larvae occur in clusters, mainly inside the ears and also around the anus. Injection of suspensions

of spleen from these field voles has produced fever in monkeys, and intratesticular injection in rabbits has produced orchitis with rickettsiae demonstrable in the parenchymal cells (Kawamura and Imagawa, 1931).

In Formosa, *T. akamushi* has again been incriminated as the vector of the disease. The larvae have been found to infest numerous species of rodents and other animals. *Rattus losea* and *Apodemus agrarius*, commonest rodents in the endemic area, are heavily infested (Morashita, 1942). Other rodents harbouring the larvae include *Rattus rattus rattus*, *R. rattus rufescens*, *R. norvegicus*, *R. coxinga*, *A. semotus*, *Mus musculus*, *M. formosanus*; and larvae have also been found on the shrew (*Crocidura murina*), the dog, ox, buffalo and some birds - fowl, pheasant, the button quail (*Turnix taigour*) and the crow-pheasant (*Centropus javanicus*). A rickettsial strain has been isolated from *R. losea* captured in the endemic area.

T. akamushi is also considered to be the vector in the Pescadores. *R. rattus rufescens* is heavily infested with larvae, and a rickettsial strain has been isolated from its tissues (Morashita, 1942).

In Sumatra a close connection has been shown between larval trombididae and the occurrence of the disease. The vector is thought to be *Trombicula deliensis*. The larva was first described by Walch (1923), but according to Gater (1930) this larva and that of *T. akamushi* are merely different forms of the same species. The differences, in the number of divisions to the claw of the pedipalp and in certain

other minute morphological details, are very slight indeed. The adult has been found for the first time, by Radford in Ceylon. Walch and Keukenschrijver (1923) found that 50% of the rats trapped in an estate where the disease was endemic harboured larvae of *T.deliensis*. Only 3% of rats from a non-endemic area were so infested. The species harbouring larvae were the Malayan house rat (*R.concolor*) and the field rat (*R.diardi*). Larvae were also found on *Acrocephalus orientalis*, a bird which migrates southward from Japan in winter. Wolff and de Graaf (1939 a) were unable to isolate any rickettsial strains from rats, but they showed that *R.rattus brevicaudatus* was capable of acting as a reservoir of *R.orientalis*, without showing any objective manifestations.

T.deliensis is also suspected to be the vector in Malaya. Fletcher, Lesslar and Lewthwaite (1928) found the larvae on rats trapped in endemic areas. Gater (1932) examined labourers on an oil-palm estate where "scrub typhus" had occurred, and removed, in 538 examinations, 87 trombidid larvae of three species, *T.akamushi*, *T.deliensis* and *T.hirsti*. Though *T.akamushi* was more common on man than *T.deliensis*, the reverse obtained in the case of rats. On town rats, trombidid larvae were rarely found, while on rats from rural areas both *T.deliensis* and *T.akamushi* occurred, the proportions being 21% and 1% respectively. The common urban rat is *Rattus rattus diardi* and the rural rat is *R.rattus jalorensis*. Lewthwaite and Savor (1936 e) isolated strains of *R.orientalis* from

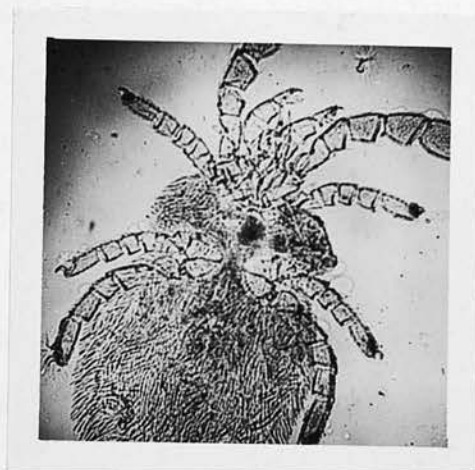


Fig.3. -Trombicula
deliensis, adult. X 33



Fig.4. -T.deliensis,
larva. X 160

rural rats, which they showed were identical in all respects with strains isolated from human sources.

In Australia, Heaslip (1941) found that 90% of the 2,500 larval mites collected from rodents captured in endemic areas were *T. deliensis*. No rickettsial strains, however, were isolated from these mites. As far as the reservoir is concerned, rickettsial strains were isolated from *Rattus conatus*, *R. rattus*, *R. assimilis*, *R. norvegicus* and *Melomys littoralis*, and from *Isodora torosus*, the bandicoot. Cross-immunity tests with these strains, rat and bandicoot, and strains isolated from human sources, showed that all were identical.

In New Guinea, Gunter (1940) believes the vector to be *Trombicula minor*. Its principal hosts are the bandicoot (*Echymipera cockerelli*); the bush fowl (*Megapodius duperryi*); the bush pig (*Sus papuensis*); the bush turkey (*Tallegallus jobiensis*); the cassowary (*Casuarus casuarus*); the bush pigeon (*Gallinolumbus jobiensis*).

No very definite evidence as to vector or reservoir has come from India. Mehta (1937) found *T. deliensis* larvae on rats, in the Simla hills, and Webster (1940), working in the same locality, found a monkey, *Simulans rhesus*, to be infested. An interesting observation by Smith and Mehta (1937) is to the effect that in the summer months in the Simla hills, when cases of the type of typhus-like disease under consideration occur, the number of rat sera containing antibodies in significant titre for *Proteus OXK* increases markedly above the number so obtained in the winter months.

Shortt and D'Silva (1936) found that cases of typhus-like disease have occurred in the Kasauli area only during the six to seven years previous to their report. About the same time the grey squirrel was introduced from Madras Presidency. Of these squirrels, 60% showed serum agglutinins for *Proteus* OXK up to a dilution of 1 in 250. On the other hand, only 2% of squirrels trapped in the plains showed similar reactions.

The vector in Ceylon is probably *T. deliensis*. The larvae have been found in large numbers on *Rattus rattus kandyanus*, the common rat of Ceylon, and have also been found on the bandicoot.

The author has carried out the following experiments:-

1. Larval *T. deliensis* were obtained from rats trapped in an endemic area. The larvae were washed in several successive changes of sterile normal saline, being recovered after each washing by centrifuging. They were then ground up and suspended in saline. The suspension was injected intraperitoneally into white mice. In all, about 150 larvae were used. No rickettsial strains were isolated.
2. Larvae, collected from rats trapped in a non-endemic area, were placed on white mice already infected with *R. orientalis*. In order to show that these larvae were not themselves infected, half of each batch was injected intraperitoneally into healthy white mice. The mice remained unaffected. Despite numerous attempts, however, the larvae

would not attach to the infected mice, the probable reason being that they had already fed, at least partially, on the hosts from which they had been obtained.

3. Attempts have been made to isolate strains of *R.orientalis* from *R.rattus kandyanus* trapped in an endemic area. Emulsions of the brains were made in normal saline and were injected intraperitoneally into white mice. Twenty one attempts have so far been made, but have been unsuccessful. In 15 of the rats the Weil-Felix reaction was carried out by Dr. L. Nicholls, and in the remainder by the author, but all were negative for *Proteus OXK* and *Proteus OX19*.
4. In order to show that *R.rattus kandyanus* is capable of acting as a reservoir of *R.orientalis*, 8 rats were injected with passage virus in the form of spleen suspensions from infected white mice. To demonstrate, as a preliminary measure, that these rats, which were trapped in an area far removed from any known endemic site did not already harbour a naturally acquired rickettsial infection, mice were inoculated in each case with heart blood withdrawn under light ether anaesthesia. Fourteen such specimens of blood were withdrawn, but only 8 rats survived for the ensuing experiments. The blood was inoculated in the form of a suspension of blood clot in saline, the serum being used for the Weil-Felix reaction. In all cases this was negative, using suspensions of *Proteus OXK* and *OX19*. None of the inoculated mice developed *R.orientalis* infection.

Two of the rats thus inoculated with passage virus were killed 15 days after the injection. No abnormalities were evident at autopsy and no rickettsiae were found in smears from the spleen, and in the case of males, from the tunica vaginalis. Suspensions of the spleen were made in each case and injected intraperitoneally into white mice. These mice died in due course from typical *R.orientalis* infection. Two more rats were killed 29 days after inoculations and again a rickettsial infection was produced in the same manner in white mice. The 4 remaining rats were killed in pairs two and three months respectively after inoculation. Mice inoculated with spleen suspension from these rats failed to develop a rickettsial infection.

Other Possible Vectors of Infection

The possibility of the transmission of *R.orientalis* by arthropoda other than mites has also received attention.

Lice.

Fletcher and Lesslar (1925) found no body lice on 472 Tamil hospital patients and labourers, though head and pubic lice were found.

Nicolle and Sparrow (1936) showed that *R.orientalis* remains active in lice for 7 days after the infected feed, but infection cannot be transmitted to susceptible animals by the bite of these insects.

Fleas.

Lewthwaite, Hodgkin and Savor (1936) were unable

to demonstrate transmission of *R.orientalis* by the rat flea (*Xenopsylla cheopis*). Nicolle and Sparrow (1936), however, found that *X.cheopis* could be infected with *R.orientalis*, and could transmit the infection to susceptible animals by its bite.

Ticks.

Fletcher and Lesslar (1925, 1926) thought that "scrub typhus" might be transmitted by the bite of a larval tick. They abandoned this view later, and considered that a larval mite was probably the vector. Lewthwaite, Hodgkin and Savoor (1936) could not obtain "definite infection" of guineapigs with *R.orientalis*, using the dog tick, *Rhipocephalus Sanguineus*, as vector. The animals did appear, however, to have developed some resistance to further infection. This was thought to have been due either to the rickettsial strain becoming attenuated in virulence by passage through ticks, or to a few rickettsiae only persisting in the ticks, and thus giving rise in the guineapigs to a feeble immunity.

Conclusions

The view that a type of typhus-like disease is transmitted by larval mites has long been held in Japan. The larval mite has been shown to belong to the genus *Trombicula* Berlese (1905) and has been named *T.akamushi*. Transmission of the disease by this larva has been shown experimentally, and nymphs, adults and larvae bred out in the laboratory from larvae captured in endemic areas have also produced infection when injected into susceptible animals.

Infection of such animals by the bite of laboratory bred larvae has also been demonstrated.

In no other country has any experimental evidence incriminating trombidid mites been brought forward. On the other hand, there are very few records of negative experiments. Heaslip's (1941) failure to isolate rickettsial strains from *T. deliensis* is one of such rare records. It would seem as if the majority of workers have been content to consider that by analogy diseases of the tsutsugamushi type are transmitted by mites. It is probable that attempts to isolate strains of *R. orientalis* from various stages in the life cycle of trombidid mites have in fact been made, but that the relatively insusceptible guineapig has usually been the laboratory animal employed. It has been pointed out, too, that though the rabbit is very susceptible to *R. orientalis* infection when injected with infected material into the anterior chamber of the eye, it often appears difficult to initiate strains. Regarding the white mouse, though it is very susceptible to infection, with some strains at least, of *R. orientalis*, it seems only to have been used as an experimental animal in this respect to any extent since 1940. Since 1941-2, of course, many of the countries where the disease occurs have been in enemy occupation. These factors may account for the lack of experimental proof of the vectorship of *R. orientalis* by trombididae in countries other than Japan.

It must be noted, however, that everywhere the problem has been studied, a close connection has been found to exist between larval trombididae and typhus-

like disease of the tsutsugamushi type. As will have been seen from the foregoing sections, the circumstantial evidence regarding mite transmission is strong. Taking this into consideration, and also the similarity of the clinical manifestations and the serological findings, and the results of cross-immunity experiments in all cases where these have been performed, it seems justifiable to regard the disease, wherever found, as typhus of the mite-borne type.

We now come to a consideration of the facts concerning seasonal variations in the incidence of the disease. In Japan, Formosa, Pescadores and the Simla hills of India, a well-marked seasonal incidence has been noted. In these areas cases of the disease occur more or less only in the summer months. In some instances the maximum number of cases occurs after the rains. On the other hand, in the islands of the Malay Archipelago the disease occurs all the year round. The explanation of these differences can be made in terms of climatic variations. Those countries in which the disease occurs in summer only do in fact have a summer which is distinguishable from the other seasons of the year. In Japan, Miyajima and Okamura (1917) considered that *T. akamushi* passed the cold weather in the adult, non-parasitic, form. The tsutsugamushi disease only occurred, therefore, in the summer months when the larvae hatched out. In the islands of the Malay Archipelago and other areas of similar latitude, on the other hand, the seasons are ill-defined and the mean temperatures and humidities vary little throughout the course of the year. It

appears likely, therefore, that the life cycle of trombidid mites continues uninterrupted by any long term of more or less inactive existence in the adult stage. Larvae would thus be hatching throughout the year, and so cases of the disease would continually occur.

The next question for consideration is that of the reservoir of infection. Rodents are everywhere incriminated, the actual species varying from country to country. But the question arises, is it necessary to regard rodents as an active factor in the persistence of *R.orientalis* in nature? We know that the rickettsial infection in mites is hereditary. The larvae feed only once and the remaining instars are neither parasitic nor predacious. Also, the author's experiments in the case of *R.rattus kandyanus*, and those of Wolff and de Graaf (1939 a) in the case of *R.rattus breviceaudatus*, indicate that rickettsial infection in these rodents is not a prolonged infection or, as it were, an indefinite carrier state, but rather a manifestation which appears to be naturally limited to a period measurable in weeks. The view may therefore be formulated that the natural reservoir of *R.orientalis* in nature is the trombidid mite, and that the rat only becomes infected as a secondary consequence of trombidid infection, in much the same way as man himself becomes infected, and in both cases the infection is of a limited nature.

If we assume, then, that the trombidid mite is the natural reservoir of infection, it would seem that rats or other rodents have no essential role in

the maintenance of the infection in nature. This is only partly true. The larval mite requires a vertebrate host for its single blood feed. Rodents are often the only vertebrates which offer such opportunities for this feed, since those areas in which trombididae occur are not constantly frequented by other types of vertebrata.

Limiting the role of the rat or other rodent to that of a host of larval trombididae which provides these insects with the necessary blood feed, and which may suffer as a result of this hospitality from a short-lived rickettsial infection, we find an explanation for certain epidemiological features of the disease. The endemic areas in which the disease occurs have been found in all countries to be sharply delimited. Were rats constantly infected with *R. orientalis* we would not expect this to be the case. We would expect to find, as a result of the migratory habits of these rodents a widespread dissemination of infection amongst trombidid mites. That this is not the case is evident from the distribution of these trombididae. Specimens of *T. deliensis* are always available at a spot situated not a hundred yards from the author's laboratory, where no cases of the mite borne type of typhus have ever been known to occur, and which is a hundred miles from the nearest known endemic area. These specimens are found both free in the soil and attached to rats and bandicoots.

SECTION V

THE WEIL-FELIX REACTION

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History of the XK strain: characteristics.

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heterologous agglutination; par-
agglutination; physico-chemical
changes in the serum .

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THE WEIL-FELIX REACTION

The Proteus X Strains

Wilson's (1909, 1910) demonstration of certain agglutinative properties of the serum of patients suffering from typhus fever has already been mentioned (Section 1).

Weil and Felix (1916), during the epidemic of typhus fever in Eastern Europe in the 1914-18 war, isolated from the urine of a patient with typhus fever a *Proteus* organism which was agglutinated not only by this patient's serum, but also by the sera of other cases of typhus. Following this, strains of *Proteus* which were agglutinable in a similar manner were isolated from the urine and blood of a number of other typhus patients. These organisms were known as the *Proteus* X strains.

The strains X1 and X2 were the first two isolated, and were used in agglutination tests during the epidemic. Agglutination with these organisms rarely exceeded titres of 1 in 500. Sixteen more strains were isolated during the course of the epidemic. Together with the first two strains they proved to be serologically identical. Collectively, these eighteen strains were designated X2. The nineteenth organism cultivated, *Proteus* X19, differed in only one respect from the X2 strains: it was agglutinated to very much higher titre by the serum of typhus patients (Felix,

1916).

When these two types, X2 and X19, were separated into their 'O' and 'H' variants the reason for this difference in agglutination became apparent. It was found that the 'O' variants differed from each other in their antigenic constitution almost completely (Weil and Felix, 1917). The two strains were thus considered to be distinct serological types. The fact that agglutinins for X19 and X2, when present simultaneously in a patient's serum could not be removed by cross-absorption tests, did not alter the position. This phenomenon was attributed to a minute overlapping in the 'O' antigen between the two types.

On the other hand, the 'H' antigen of both X19 and X2 was found to be common to the 'H' variant of both types, and in addition varying degrees of community of the 'H' antigen were found between these X strains and a number of strains of *Proteus vulgaris*. None of these latter organisms, however, contained the X19 and X2 'O' antigens. The 'O' antigens of the X strains were therefore considered to be specific to these organisms.

Proteus XK.

In 1921 a typical strain of X19 was obtained from the National collection of Type Cultures by the Bland-Sutton Institute, and was taken out to the Straits Settlements by Dr. A. N. Kingsbury in 1923. This strain was used, together with another strain of *Proteus* X19, the Warsaw strain, in agglutination tests with sera from cases of the typhus-like diseases of Malaya (Fletcher and Lesslar, 1926).

It was found that though the serum from cases of the "urban" type of tropical typhus reacted with the Warsaw strain of *Proteus* X19, no agglutination was obtained when the strain from the National Collection of Type Cultures was used. On the other hand, serum from cases of the "rural" or "scrub" type of tropical typhus agglutinated the latter strain in high dilutions.

Examination of this strain, which was called the "Kingsbury" strain, showed it to differ from typical X19 cultures in certain respects. It did not produce indol, nor did it ferment saccharose or maltose as did the typical X19 strains, salicin was not fermented (Wilson, 1927), and in addition, though it resembled Loghem's anindologenes group of *Proteus*, it was the only anindologenic strain of *Proteus* which was agglutinated by the serum of cases of typhus-like disease.

Felix and Rhodes (1931) carried out further examination of the "Kingsbury" strain and found that its 'H' antigen was, in part, identical with that common to all X strains, while its 'O' antigen was completely different from the 'O' antigens of both *Proteus* X19 and *Proteus* X2, not even showing that slight degree of community with these latter, which they possess between themselves. These workers came to the conclusion that the "Kingsbury" strain was a variant of the X19 culture originally obtained from the National Collection of Type Cultures, and represented another type of *Proteus* X. They designated it *Proteus* XK.

It has already been mentioned in Section II how it was originally considered that in addition to "urban" typhus, two other typhus-like diseases, similar to each other in many respects but differing in others, were considered to occur in Malaya. One of the points of difference between these two diseases the tsutsugamushi disease and "rural" or "scrub" typhus, was the observation that serum agglutinins for Proteus OXK formed in high titre in the case of "scrub" typhus but only in very low dilutions in the case of the tsutsugamushi disease. However, Wolff (1931) and other workers could find no differences in the titre of serum agglutinins in these two apparently separate conditions, and for this and other reasons it ultimately came to be recognised that the tsutugamushi disease and "scrub" typhus were in reality the same disease entity, one of the characteristics of which was the formation of antibodies to Proteus OXK in high titre. This was also found to be the case when the test was applied to the tsutsugamushi disease in Japan and to similar conditions elsewhere.

The Nature of the Weil-Felix Reaction

There has been a great deal of discussion as to the nature of the Weil-Felix reaction. Some of the main theories only will be mentioned here. Weil and Felix (1918, 1921) considered the reaction to be of a specific nature: they demonstrated a measure of antigenic community between R. prowazeki and Proteus OX19, and considered that Proteus OX19 might be a

saprophytic stage in the life cycle of the rickettsiae.

Wilson (1920, 1927, 1930) regards the Weil-Felix reaction as an example of heterologous agglutination. Proteus X19, he states, is only one, though the most suitable, of a number of organisms which can be used for diagnosing typhus fever. He allows, however, that agglutination of Proteus X19 might occur in typhus fever because the typhus virus and Proteus X19 (and certain other bacteria) contain an antigen in common.

Various other theories have been elaborated to account for the Weil-Felix reaction - physico-chemical alterations in the serum of typhus patients, the theory of paragglutination, and others. Reviews of the literature and discussions of these theories have been published by Wilson (1920, 1927) and Felix (1931).

In any event the Weil-Felix reaction is sufficiently specific, clinically, to be a valuable laboratory test in the diagnosis of the diseases of the typhus group, providing certain precautions be taken and certain limitations of the test be kept in mind.

Sources of Error in the Interpretation of the Weil-Felix Reaction

The remarks which follow are applicable to the Weil-Felix reaction as carried out with any of the Proteus strains as antigen, but particular attention has been given to the test as performed with suspensions of Proteus OXK.

1. Presence of 'H' antigen in suspensions.

Only pure 'O' suspensions should be used. This

requires frequent checking of the Proteus cultures from which the suspensions are made, since there is always a tendency for 'H' forms to appear, especially in the case of Proteus XK.

Should there be 'H' antigen in the suspension errors are likely to occur since previous or existing infection with Proteus vulgaris may give rise to 'H' antibodies. As already noted, the 'H' antigens of the Proteus X strains and Proteus vulgaris correspond to a considerable degree.

2. Occurrence of "non-specific" 'O' antibodies

'O' antibodies may occur in the serum in conditions other than the typhus group of fevers. Dinger (1934) reports two cases of urinary infection from which organisms culturally identical with Proteus XK were isolated. In each case serum agglutinins for Proteus OXK were present. Dammin and Billings (1942) have found 'O' agglutinins for the three types of Proteus X in cases of infection with Proteus mirabilis and Proteus vulgaris. Agglutination of Proteus OXK up to titres of 1 in 640 have been observed. It is interesting to note that such serum agglutinins appear only in patients who develop appreciable titres for their own organism.

Gratch (1943) reports another type of case in which 'O' agglutinins for Proteus X19 develop. Pregnant women are said to show such serum reactions, and in those women who were not pregnant, and in men in whom the reaction was positive, carcinoma was present. It seems, therefore, that the specific molecular grouping which is the OX19 antibody can be

produced as a response to disturbances other than infection - possibly of a metabolic nature.

3. Inhibitory zones.

Inhibitory zones covering the 1 in 25 and 1 in 50 dilutions are often found in unheated sera. If sera for the test be first heated for 30 minutes at 45 deg. C. the zone effect may be abolished. (Felix 1944).

4. The two types of agglutinin curve.

Two types of agglutinin curve are known to occur in typhus fever. In one type of curve the agglutinins for *Proteus* OX19 appear early, the maximum titres are high and a raised titre persists for a long time after recovery. In the second type of curve the agglutinins appear comparatively late, the maximum titres are low and the agglutinins disappear early in convalescence. Felix (1944) points out that the usual incubation of 4 hours at 52 deg. C. employed in the Weil-Felix test may destroy the low titre agglutinins completely. He therefore advocates incubation for 2 hours at 37 deg. C. followed by 22 hours at room temperature or in the ice-chest. This procedure results in somewhat lower end-titres but the low titre agglutinins are preserved. He suggests that similar precautions should be taken in the case of mite borne typhus.

5. Normal serum agglutinins.

The question of normal serum agglutinins will be considered in relation to *Proteus* OXK only.

Various workers have found serum agglutinins for *Proteus* OXK in healthy persons up to levels which differ considerably. Lewthwaite and Savor (1940)

have taken agglutination in a dilution of 1 in 125 as an arbitrary lowest limit for a positive reaction, but only where there has also been clinical evidence of infection. Boyd (1935) found serum agglutinins for *Proteus* OXK in dilutions of 1 in 25 and 1 in 50, but rarely higher. Gunter (1937) considered that a titre of 1 in 80 by the end of the first week of the disease constituted a positive reaction. Pomales-Lebron and Morales-Otero (1942) found serum agglutinins for *Proteus* OXK in healthy persons as follows: Agglutination in a dilution of 1 in 25 in about 80% persons, 1 in 50 in about 20%, 1 in 100 in about 3%, 1 in 200 in about 1.5%, 1 in 400 in about 0.5%, no agglutination in about 20%. Smith and Evans (1943) examined 11 patients suffering from non-typhus diseases. The results were: Agglutination in a dilution of 1 in 25, one patient, 1 in 50 in 2, 1 in 125 in 2, 1 in 250 in 3, 1 in 315 in 3, 1 in 415 in 1.

It is thus evident that 'O' agglutinins for *Proteus* OXK may be present in the sera of normal patients, and of patients suffering from certain *Proteus* infections, in, at times, quite high dilutions. When interpreting the results of the Weil-Felix reaction, therefore, these facts must be borne in mind, and the results should be evaluated in the light of the clinical condition of the patient. Demonstration of a rising titre in two or more successive tests is the most satisfactory evidence on which to decide that the serological reaction is positive.

The Weil-Felix Reaction in Mite Borne Typhus

The following paragraphs contain an account of the author's findings.

Technical data

Suspensions: Concentrated alcoholic suspensions of pure 'O' strains of the three Proteus organisms, issued by the Enteric Laboratory, Kasauli, were employed. Each batch of suspension was issued with a sensitivity factor, which was applied when noting the results.

Serum: Unheated serum was used.

Dilutions: Doubling dilutions from 1 in 20 upwards were employed.

Incubation: The tubes were placed in the water bath at 52 deg. C. for 4 hours, and then allowed to remain at room temperature overnight.

Reading of Results: The last trace of agglutination visible to the naked eye was taken as the end-point.

Results of the test: Agglutination in a dilution of 1 in 160 was taken as the lowest limit to constitute a positive reaction. A single test giving such a result was taken as a "positive Weil-Felix reaction" and further tests were not performed, if the patient's clinical condition was typical of mite borne typhus.

Where, however, the clinical appearances left room for doubt, a rising titre for Proteus OXK was always demonstrated, no matter what the initial reading happened to be, and the possibility of diseases other than mite borne typhus was excluded clinically and by laboratory tests. Particular attention was paid to those cases in which the reaction remained negative throughout.

Sera from 417 patients were examined with the following results:-

Number positive: 333

Number negative: 84

Positive sera

Of the 333 positive cases 232 were positive on the first test between the 8th. and 45th. days of the disease. The remaining 101 cases in whom positive serological results were obtained did not give positive reactions at the first test. Subsequent tests were therefore performed at intervals till the reaction became positive. Table 7 shows the results, giving the day of the disease with the number of patients whose sera were positive for the first time on that day. In each case there had been no agglutination in the preceding test which had been performed not more than 5 days previously, or alternatively, the first test had shown agglutination in a dilution of lower than 1 in 160, while the next, positive, test showed that the titre had risen. Included in the table are the two cases in which the test was positive on first examination on the 5th. day of the disease.

Reference to Table 7 shows that about half the patients exhibit a positive reaction for the first time between the end of the second and the end of the third week of the disease (49 patients first showed a positive reaction between the 12th. and the 20th. days), though in each case, of course, the reaction could have appeared 4 days earlier than the table shows. The incidence of the remaining positive reactions falls fairly evenly between the 5th. and 45th. days (no tests

were done before the 5th. day or after the 45th.).

Table 7

Column A: Day of disease

Column B: Number of positive
cases

A	B	A	B	A	B	A	B
5	2	14	5	22	1	32	2
7	4	15	1	24	3	33	2
8	3	16	5	25	1	34	1
9	1	17	5	26	7	35	3
10	1	18	9	27	3	42	1
11	3	19	3	28	1	43	1
12	11	20	4	29	3		
13	6	21	2	30	4		

Negative sera

Eighty four patients showed negative Weil-Felix reactions despite the fact that several tests were made in each case. As has been mentioned, particular care was taken in these cases to ascertain that clinically their condition was that of mite borne typhus. The relevant facts concerning these cases are given in Table 8.

Regarding consistently negative Weil-Felix reactions, other workers have had varied experiences. However, the present observations comprise a larger number of cases than have been published in the literature up to date. Wolff (1931) found 15 cases with a negative reaction out of 45 cases, but some of these were not adequately tested. Lewthwaite and Savoor

Table 8

Column A: First and last days on which tests were made.

Column B: Number of tests made.

Column C: Approximate interval in days between tests.

A	B	C	A	B	C
8-29	6	4	14-34	4	6
8-30	5	5	14-35	4	6
7-29	6	4	12-32	4	6
13-35	5	5	11-36	3	12
12-33	5	5	13-37	3	12
8-29	5	5	10-35	3	12
7-30	4	7	10-35	3	12
11-29	3	9	10-33	4	7
11-30	3	9	14-40	4	8
12-31	3	9	10-31	3	10
12-29	3	8	10-30	4	6
13-32	3	9	14-43	3	14
13-33	3	9	13-42	3	14
14-33	4	6	14-40	3	12
13-33	3	9	13-41	3	13
8-27	4	6	14-40	3	12
9-29	4	6	11-40	3	14
12-40	5	7	12-40	4	9
13-32	4	6	11-39	3	13
10-31	4	6	13-33	3	10
14-42	4	9	9-31	4	7
14-37	4	7	11-31	4	10
10-35	3	12	14-30	3	8
9-47	5	9	10-29	3	9
7-40	5	8	12-39	3	13

Table 8 (Contd.)

A	B	C	A	B	C
12-34	3	10	15-42	3	13
12-45	6	6	9-29	3	9
12-32	3	10	14-33	4	6
11-32	3	10	11-33	4	7
10-35	4	8	10-32	4	7
11-28	3	8	10-33	3	11
12-34	3	10	13-35	4	7
12-28	3	8	12-35	4	7
8-22	4	4	10-38	3	14
21-42	5	5	21-36	3	7
8-19	4	3	21-35	3	6
17-32	3	5	20-39	4	6
16-29	3	6	20-40	3	10
16-31	3	7	19-30	3	5
16-39	3	11	17-38	3	10
18-39	3	10	16-37	3	10
18-39	3	10	16-42	3	12

(1940 b) state that a consistently negative Weil-Felix reaction is rare, while the Bulletin of the United States Army Medical Department mentions cases in which the Weil-Felix reaction was negative though rickettsial strains were isolated from the patients.

The author makes the following criticisms of his results:-

1. If, as Felix (1944) suggests, a low titre type of agglutinin curve sometimes occurs in mite borne typhus, then incubation at 52 deg. C. may have destroyed these apparently heat-sensitive agglutinins.

2. Reference to Table 7 shows that an appreciable number of cases develop a positive reaction for the first time on or after the 29th. or 30th. day. In the majority of cases shown in Table 8 the last test was made between the 29th. and 37th. days. In only a few cases were tests made up till the 40th., and in a very few, the 47th., day.

3. In a number of cases the interval between tests was possibly long enough to allow a rise and fall of titre to remain undetected.

A combination of these factors may account for the number of patients showing negative reactions.

Conclusions

In patients suffering from mite borne typhus the serum develops agglutinins for Proteus OXK. These agglutinins appear for the first time between the end of the second and the end of the third week in about 50% of cases who develop such agglutinins.

Under the conditions of test employed by the author about 20% of the total number of cases tested showed a negative Weil-Felix reaction. The causes for this are discussed. In some cases it appears that low titre agglutinins may have developed but escaped notice. In others, owing to the necessity of discharging patients from hospital at the earliest possible time, tests were discontinued before the end of the period during which agglutinins are known to make their first appearance.

SECTION VI

PATHOLOGY

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PATHOLOGY

Autopsy material from 13 cases has been studied. The specimens were received in 5% formol saline, and paraffin sections were prepared in the usual manner. Sections were stained with Ehrlich's haematoxylin and eosin.

The remarks on the morbid anatomy have been compiled from the post-mortem notes sent with the specimens.

General Appearances

In most cases post-mortem rigidity and lividity were noted as present, and showed no unusual features. An eschar was present in 5 cases, but no specimens were sent for histological examinations.

Cardiovascular System

Morbid anatomy.

In 6 cases the heart was described as normal. In the remaining cases there was some right sided dilatation and the myocardium was softer and paler than normal. In all cases the pericardium, endocardium, valves and vessels were normal.

Morbid histology.

Myocardium.

In every case there was an interstitial cellular infiltration. The majority of the cells were

lymphocytes. Mononuclears were also present in fairly large proportion, but were not quite so numerous. Occasionally a plasma cell was seen, and very rarely a polymorph was present.

The mononuclear cells were for the most part rather small, the nucleus being about the same size as that of a lymphocyte, and almost as dark and condensed in appearance, while the total cell diameter equalled that of a polymorph. In addition, larger mononuclears with a more abundant cytoplasm often containing cellular debris were seen. The smaller type of cell showed very strong affinity of the cytoplasm for the acidophilic stain.

This cellular infiltration was never diffuse. In some cases it was represented by only a few cells lying between the muscle fibres, while in others the infiltration was more copious. Serial sections, however, and the comparison of various areas, showed that the patchy nature of the infiltration was due to the vascular origin of the cells. Commencing in the coats of the smaller blood vessels, the infiltration spreads out in the interstitial tissues, becoming less marked as the distance from the site of origin increases. In addition, the vascular and perivascular infiltrations were not evenly distributed throughout the length of the vessels, but occurred at localised points only. Thus, in any particular section, a vessel showing infiltration may be located in juxtaposition to a vessel showing no such cellular accumulations.

The heart muscle itself showed no severe degree

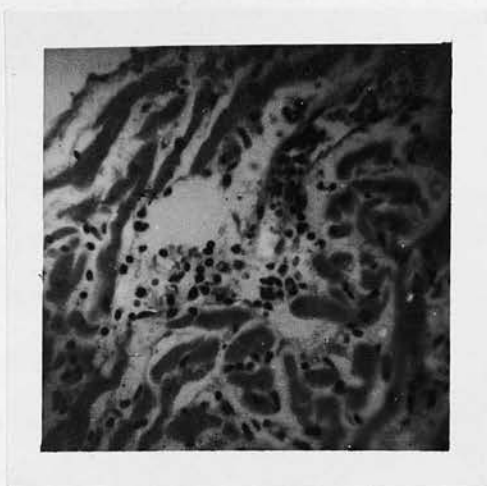


Fig.5. -Perivascular infiltration in the myocardium. X 160

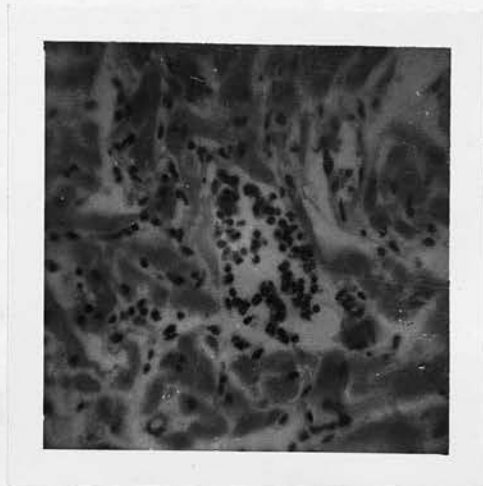


Fig.6. -Interstitial infiltration in the myocardium. X 160

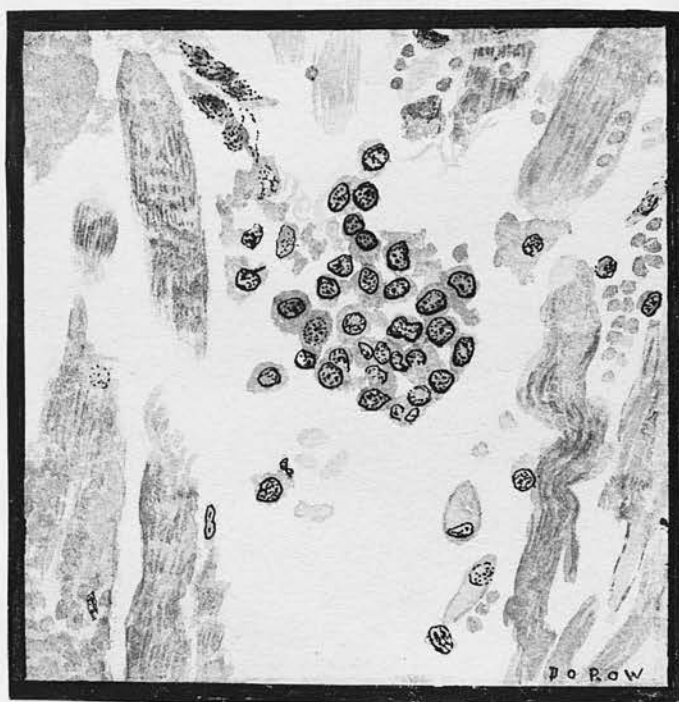


Fig.7. -High power view showing the character of the infiltration. Practically all the cells seen here are mononuclears.

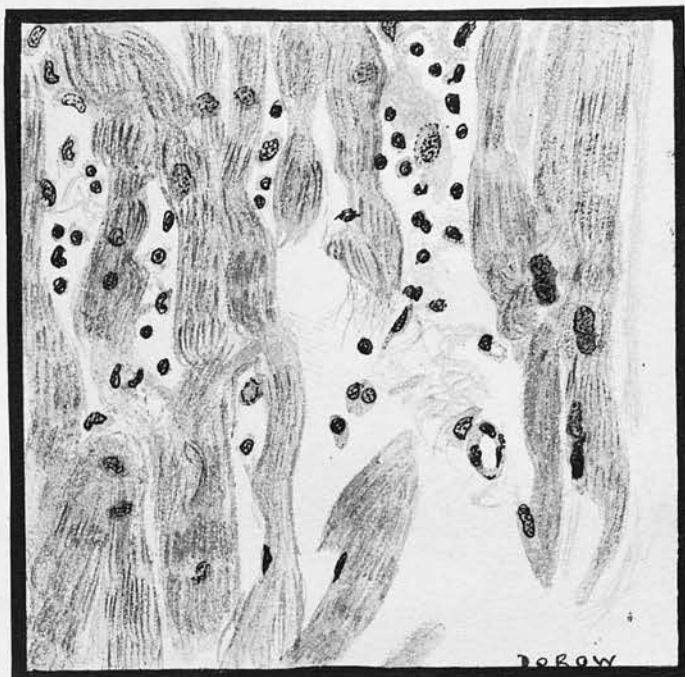


Fig. 8. -Interstitial cellular infiltration in the myocardium. The cells in this field are mainly lymphocytes. Some mononuclears are also present.

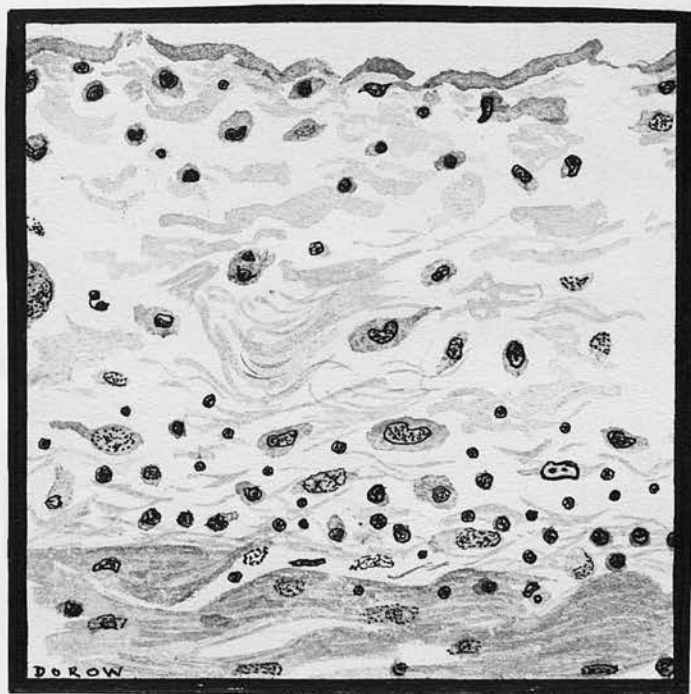


Fig. 9. -Infiltration of lymphocytes and mononuclears in the pericardium.

of change. All cases showed cloudy swelling with some loss of definition in striation. There was no destruction of fibres anywhere.

Blood vessels.

The changes in the blood vessels have already been indicated. In all cases the large coronary branches were normal, the cellular infiltrations being seen in and around the arterioles and the pre-capillaries. These vessels, at the affected points, showed some swelling of the endothelial cells. There was an infiltration of the media, and to a greater extent, of the adventitia, with mononuclears. The structures composing the vessel walls otherwise remained normal. No occlusions or obliterations were seen.

Pericardium.

In most cases the pericardium was normal, or practically so, showing perhaps the presence of a few lymphocytes and mononuclears. In one case, however, there was a rather more extensive infiltration, and in a further two cases the infiltration was quite marked. The cells were the same as those seen in the myocardial interstitial tissues - lymphocytes and mononuclears - and the infiltration was, in places, continuous with the cellular accumulations in the myocardium along the fibrous septa passing inwards from the pericardium.

Endocardium.

No abnormalities were found.

Large Vessels

In one case there was femoral thrombosis.

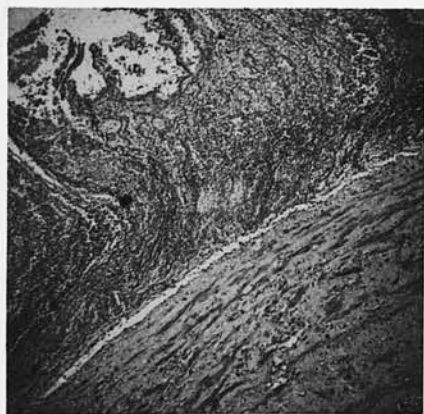


Fig.10. -An organising
thrombus in the femoral
vein. X 33

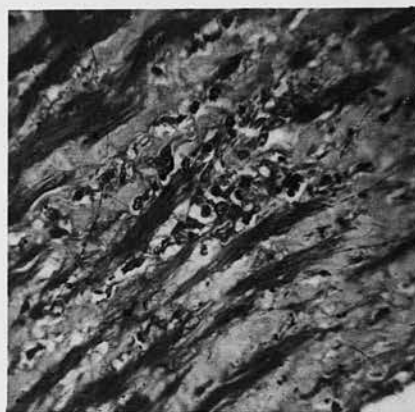


Fig.11. -High power view
of the media of the vein
shown in Fig.10. Infil-
tration of lymphocytes
and mononuclears around
the vasa vasorum. X 160

Sections of the vessel showed commencing organisation of the thrombus. The vessel wall showed a slight infiltration of lymphocytes and mononuclears around the vasa vasorum in the media.

Respiratory System

Morbid anatomy.

The lungs showed pathological changes in all cases. In 8 cases the lungs were described as congested and oedematous, though without evidence of infection, while in the remainder infection was present in varying degree as follows:-

1. Left lower lobe firm and oedematous, with several foci of bronchopneumonia. Right lower lobe showed bronchitis but no bronchopneumonia.
2. Right upper lobe showed diffuse grey hepatization. Lower lobe showed bronchopneumonia. Left upper lobe normal. Lower lobe showed bronchopneumonia.
3. Right lower lobe showed a recent abscess. Left lower lobe showed bronchopneumonia and infarct.
4. A left haemopneumothorax was present, with about $1\frac{1}{2}$ pints of blood in the pleural cavity. A recent abscess was present in the lower lobe. The right lung was congested and oedematous, with bronchopneumonic patches of consolidation in both lobes. An infarct was present at the base.
5. Bronchopneumonia of both lower lobes

Morbid histology.

The cases in which there was no evidence of bacterial infection on naked-eye examination will first be described. These will be numbered as cases 6 to 13.

Cases 6 and 7 showed similar appearances. There was very marked congestion, the alveolar walls thus presenting a rather beaded appearance. They also showed a moderate degree of infiltration with lymphocytes and mononuclear cells, and some oedema. The capillaries themselves, apart from congestion, were normal. The arterioles and venules in the septa often showed a rather scanty infiltration of the adventitia with mononuclear cells. The alveolar spaces contained an occasional erythrocyte and large mononuclear phagocyte. The bronchi showed some desquamation of the epithelium. The pleura showed a scanty infiltration with lymphocytes.

In Case 8 the same congestion was seen, but here the alveolar spaces contained oedema fluid. In some there was fluid only. Most contained in addition moderate numbers of erythrocytes and large mononuclear cells. The bronchi showed acute inflammation, but there was no extension of infection into the lung tissue.

Case 9 showed similar features, congestion, fluid exudate and the presence of red cells and large mononuclears in the alveoli being the main findings.

Case 10 showed a bronchopneumonic process with polymorphic exudate, red cells and mononuclears in the alveoli. This inflammation was localised to small areas around the bronchioles, and gave the impression of being a recent, and secondary, inflammation superimposed on a condition of intense congestion similar to that found in the cases already described. The interlobular septa showed infiltration with lymphocytes, mononuclears and occasional plasma cells.

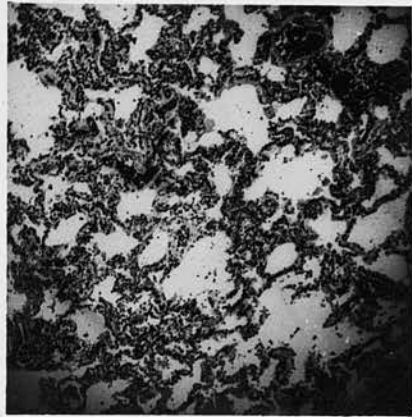


Fig.12. -Lung. Much congestion with escape of red cells into the alveoli. X 33



Fig.13. -Lung. In addition to the congestion there is serous and cellular exudation into the alveoli. X 33

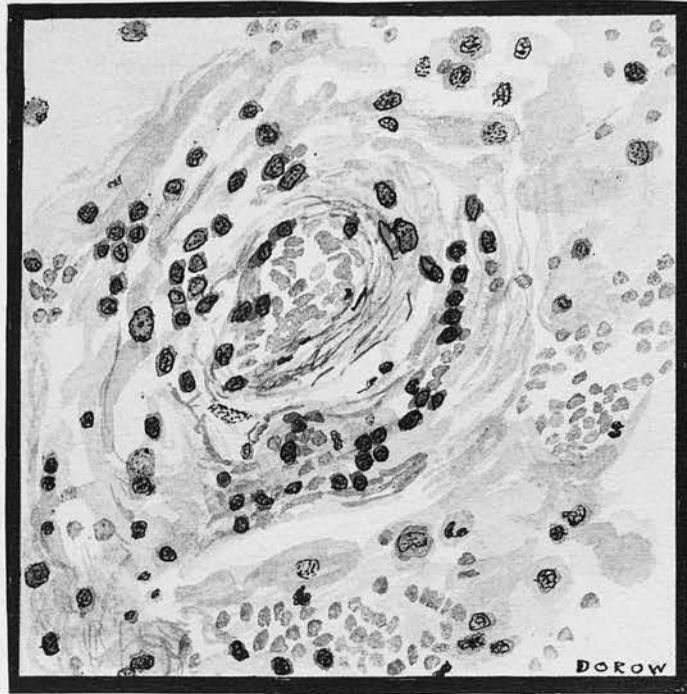


Fig. 14. -A septal arteriole in the lung, showing infiltration of the media and adventitia with lymphocytes and mononuclears.

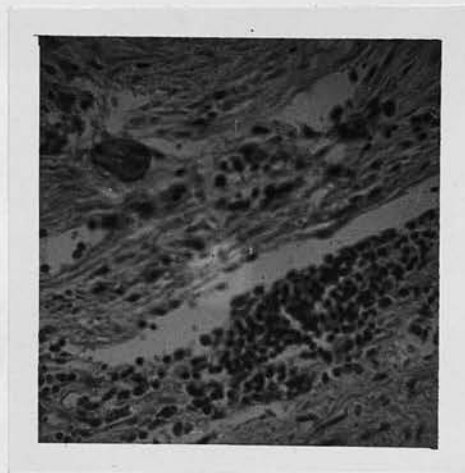


Fig.15. -Spleen. An accumulation of lymphocytes and mononuclears in a trabecula. X 160

Polymorphs were almost entirely absent. This infiltration was centred chiefly around the septal vessels, though it extended along the septa also. The pleura showed a similar condition. The vessels were congested and perivascular infiltration was noted.

In case 11 there was also an early bronchopneumonic. Here again, the inflammatory condition appeared to be superimposed upon a basis of intense congestion.

The remaining cases, 1 to 5, are those in which there was an obvious septic process on naked-eye examination. The histological findings confirmed the nature of the macroscopic appearances, there being no unusual features in the lobar and bronchopneumonic processes found in the various specimens.

Sections taken from those parts of the specimens which were as yet unaffected by the inflammatory process showed appearances similar to those described in the first eight cases, the main features being congestion and perivascular infiltration around the septal vessels.

The Spleen

Morbid anatomy.

In 11 out of the 13 cases the spleen was enlarged, the increase in size varying from $1\frac{1}{2}$ times to 8 times that of the normal. In each case the organ was described as being of softer consistency than normal.

Morbid histology.

The microscopic appearances in all the cases were similar. The capsule and trabeculae were, in

most instances, normal. In two cases there was some increase. All specimens, however, showed cellular infiltrations in the trabeculae to a varying extent, consisting of lymphocytes and mononuclears, with an occasional plasma cell. These cellular accumulations were disposed in small groups between the fibres of the trabeculae, and also occurred, though to a much lesser extent, in the capsule.

The veins of the trabeculae showed the most prominent changes. Many of them showed an infiltration, chiefly of mononuclear cells, just beneath the endothelium. In some cases this consisted of a single row of cells, rather widely separated, but often the cells were much more numerous, producing a complete subintimal "collar".

The arterioles showed less marked changes. There was occasionally some swelling of the endothelium, and in most cases there was an infiltration of the media, and adventitia, and perivascular tissues, consisting of lymphocytes and mononuclears.

In all cases there was proliferation of the reticulum cells. The pulp spaces were much congested in all cases. The sinuses contained numerous erythrocytes and mononuclear cells. The littoral cells were hyperplastic, and the free macrophages in the sinuses showed very active erythrophagocytosis

The Malpighian bodies were rather small and tended to be ill-defined. In two cases they showed central degeneration with nuclear fragmentation. The central arterioles were normal. A third case showed foci of necrosis scattered throughout the pulp.

Lymph GlandsMorbid anatomy.

At post-mortem examination the cervical, axillary, inguinal, paratracheal and para-aortic glands were described as enlarged, in most cases. The glands were rather softer than normal, and were discrete. A number of glands were also obtained at biopsy. In all, fortytwo specimens were examined.

Morbid histology.

Vascular congestion was a prominent feature in practically all specimens, and much dilatation of the sinuses also made an immediate impression on examination with the low powers.

Examining the glands in detail, the main findings were as follows:-

The capsule and trabeculae, normal in most cases, were usually increased in thickness in specimens obtained from the inguinal region. Collections of lymphocytes between the fibres were often seen.

The germinal centres were well-defined though they were not enlarged. Central activity was seen in a minority of cases only.

There was proliferation of the reticulum cells, and hyperplastic littoral cells lined the dilated sinuses. The sinuses contained much debris, occasional erythrocytes and fair numbers of large phagocytic mononuclears.

Tonsils

Two specimens were examined. At post-mortem examination these had been found to be enlarged.

Microscopic examination showed the picture of sub-acute tonsillitis. There were no unusual features.

Pancreas

Three specimens were examined. Two of these were normal. The third specimen was practically so, showing only a scanty lymphocytic and mononuclear infiltration around the small vessels in the interlobular septa.

The Liver

Morbid anatomy.

The liver was described as being a little enlarged in one case. In the remaining cases it was normal in size, but on section pallor was usually noted.

Morbid histology.

The microscopic appearances were similar in all cases. The capsule was normal and there was no increase in the portal connective tissue. There was, however, an infiltration of the portal tracts in every case, of more or less marked degree. The cells were mainly lymphocytes. A few mononuclears were also present. The vessels and bile ducts were apparently normal.

The parenchymal cells showed a variety of degenerative changes. In 8 cases these changes had not progressed beyond cloudy swelling, but in the remainder there was fatty change of a mild to moderate degree. In two cases the vacuoles were distributed throughout the lobules, while in the remaining

three cases they were more or less confined to the peripheral and central zones.

The Kupffer cells were enlarged in all specimens. They commonly contained pigment, cellular fragments and red cells.

Suprarenals

Three specimens were examined. No changes other than those which could be ascribed to post-mortem autolysis were found.

Kidneys

Morbid anatomy.

In 9 cases the kidneys were normal on naked-eye examination. In 4 cases they showed definite enlargement with pallor of the cortex and congestion of the medulla, which were sharply differentiated.

Morbid histology.

In those cases which were normal macroscopically, microscopic examination showed the changes of cloudy swelling.

In the remaining 4 cases, a distinctive lesion was present. This lesion consisted of an acute process affecting the kidney in a patchy manner. Though no nephrons escaped some were much more severely affected than others, and the tubules showed a greater degree of damage than did the glomeruli.

Glomeruli.

A few glomeruli were comparatively normal but most showed a greater or lesser degree of change. The tufts were generally somewhat swollen, though not

sufficiently so to fill their capsules. The epithelium of the capillary loops was also somewhat swollen, though again this was of insufficient degree to render the tufts bloodless.

The epithelium lining Bowman's capsule was almost always swollen and quite often cells had been shed into the capsular spaces. The capsular spaces themselves contained some material. Sometimes this was granular debris with which was intermingled a few red cells and an occasional desquamated epithelial cell. Usually, however, the capsular contents consisted of amorphous, intensely acidophilic material.

Tubules.

The tubules showed more severe degrees of change than did the glomeruli, and the changes were essentially of a patchy nature.

In a nephron showing a severe degree of change the ascending limb of Henle's loop and the convoluted portion showed swelling of the lining epithelium. Many of the cells contained numerous coarse hyaline and acidophilic granules, and their free borders were, to a large extent, shed off. The nuclei had usually quite disappeared. Of those that remained the majority were pale and rather swollen while some were pyknotic.

Side by side with nephrons showing these tubular changes were elements in which the tubules were dilated and lined by flattened epithelium. These dilated tubules often contained amorphous, acidophilic material of hyaline appearance, with an occasional erythrocyte and desquamated epithelial cell.

Interstitial tissue.

The interstitial tissue showed oedema in all

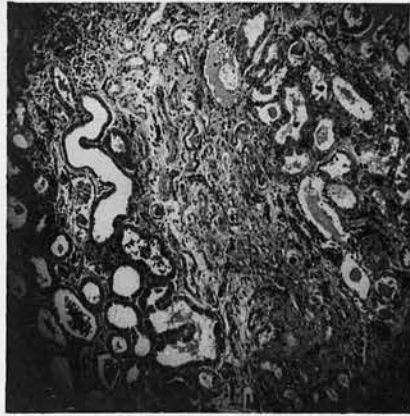


Fig.16. -Kidney. The patchy nature of the lesion is shown. X 33



Fig.17. -Interstitial oedema and infiltration. Most of the tubules in this field are dilated and contain acidophil material.

X 33

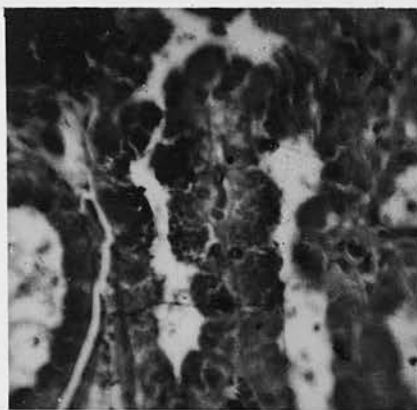


Fig.18. -Degeneration of the tubules. The cells contain hyaline granules and many have lost their nuclei. X 160

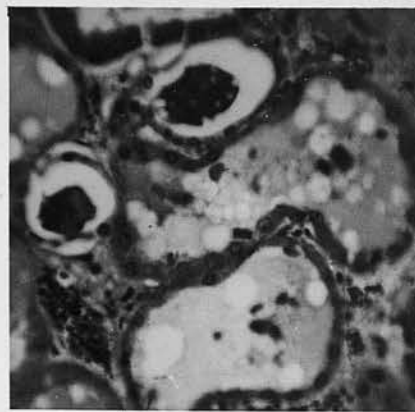


Fig.19. -In contrast to the tubules in Fig.18, these are dilated and are lined by flattened epithelium. X 160

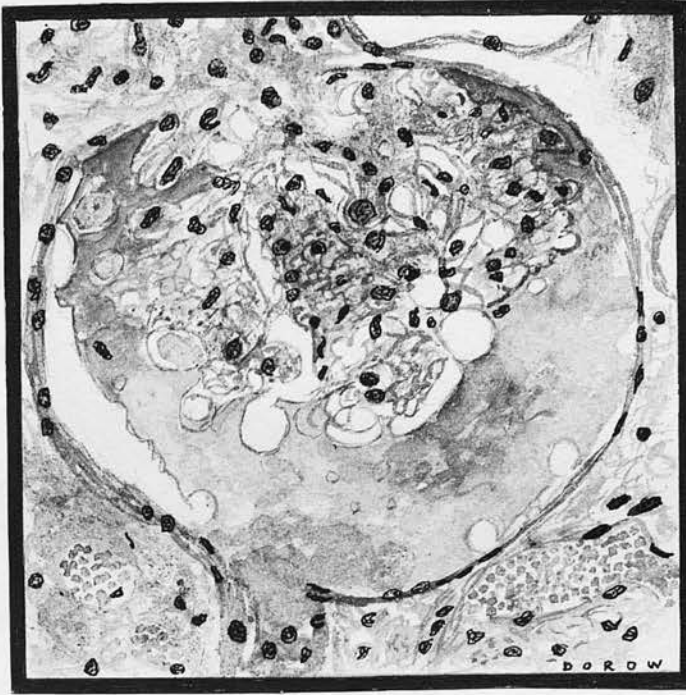


Fig.20. -High power drawing of a glomerulus. The capsular space is filled with amorphous, highly acidophilic material. The capillary epithelium of the tuft is slightly swollen. In this case the epithelium of Bowman's membrane is normal.

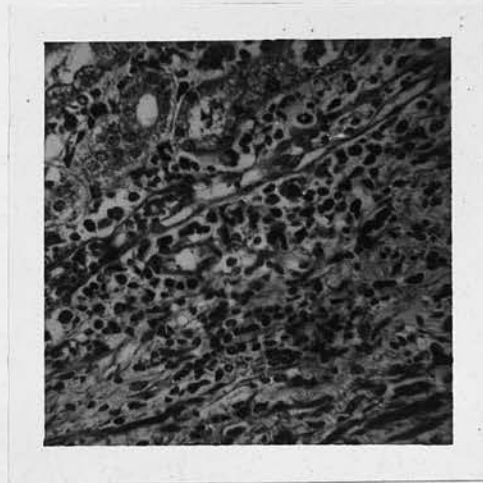


Fig.21. -Cellular infiltration in the interstitial tissue of the kidney. X 33

areas, the tubules thus being separated, sometimes quite widely. Cellular infiltration was a well-marked feature. The majority of the cells were lymphocytes, mononuclears were also quite numerous, and plasma cells were not infrequently noted. The infiltration was most marked in the perivascular areas, though periglomerular accumulations and intertubular infiltrations of larger extent were also present.

Blood vessels.

The larger blood vessels were normal. The capillaries were engorged and small haemorrhages into the interstitial tissue were quite frequent. The cortical arterioles showed the greatest changes. Round these vessels the cellular infiltration was mainly centred and many of them showed infiltration of the media and adventitia. The glomerular arterioles were normal.

Voluntary Muscle

Three specimens of voluntary muscle were examined. In one case haemorrhage into the rectus abdominalis had been found at post-mortem examination. Microscopic examination showed Zenker's necrosis. Most of the fibres in the affected area lacked definition in striation, while occasional elements showed complete disappearance of the cross-markings. These fibres took up the acidophilic stain more intensely than those which were comparatively less affected, and showed a hyaline appearance. Much haemorrhage was also present.

In the second case a portion of psoas muscle



Fig.22. -Destruction and
infiltration in striated
muscle. X 33

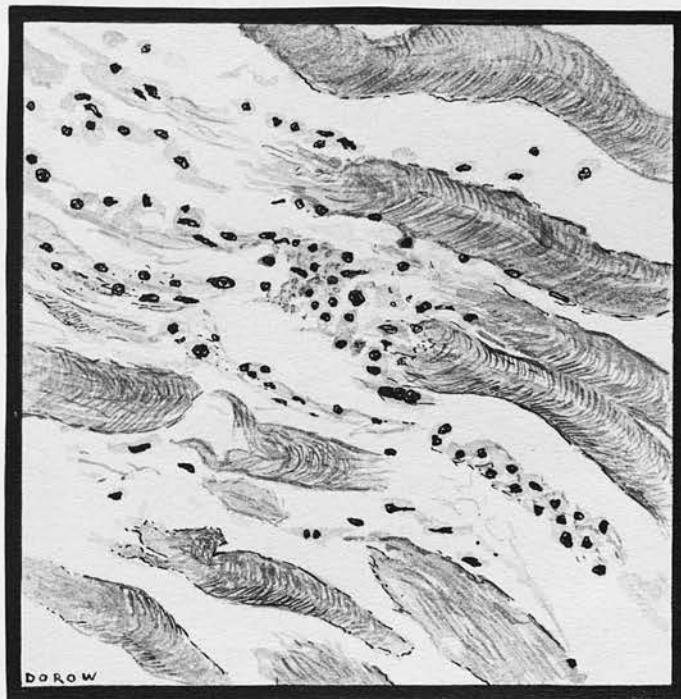


Fig.23. -High power drawing from an
area in Fig.22.

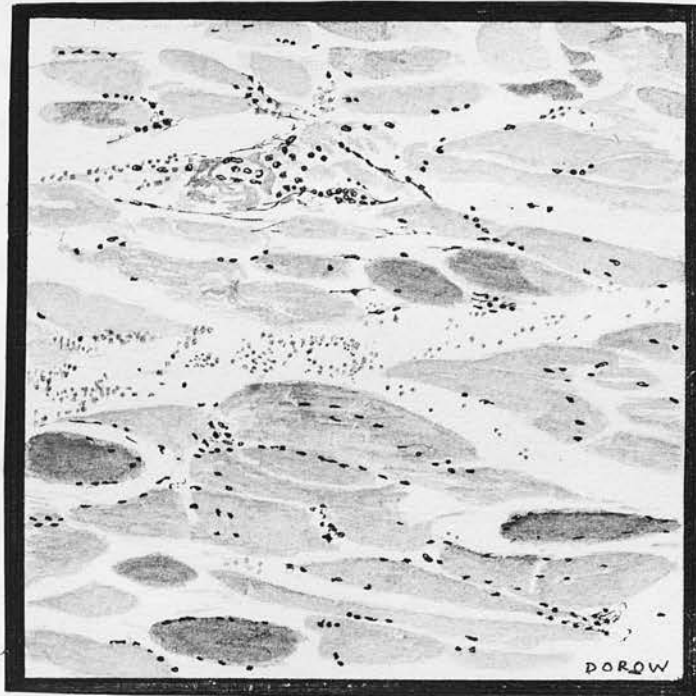


Fig.24. -Zenker's necrosis. The dark fibres represent those which were hyaline and structureless. There is much haemorrhage (light cells) and there is also an infiltration of lymphocytes and mononuclears.



Fig.25. -Parietal cortex. A capillary showing perivascular infiltration. There is also a slight increase in glia cells in the adjacent white matter. X 160

was examined. This had been requested as a specimen, since it was thought that changes in the blood vessels might advantageously be studied in this tissue. At post-mortem examination, the muscle appeared normal, and a portion was selected at random. Microscopic examination showed the presence of a destructive lesion in the muscle fibres. The fibres at the affected point showed necrosis, the debris being infiltrated with mononuclears and lymphocytes. The small blood vessels showed scanty perivascular infiltration with the same type of cells.

In the third case, again psoas muscle, no abnormalities were found.

Central Nervous System

Entire brains from 6 cases were examined. These were hardened in formol saline and subsequently sections were taken from the parietal and occipital cortex, the basal ganglia, periaqueductal grey matter, midbrain, pons, medulla and cerebellum.

No gross changes were seen except in one case in which a subarachnoid haemorrhage was present.

Morbid histology.

Lesions were found in every case, but were scanty. They were most readily found in the midbrain and consisted essentially of swelling of the capillary endothelium and a perivascular gliosis. This was never of any great extent. A row of perhaps two to three cells in depth would be present around the capillary. Occasional perivascular haemorrhages were present. Lewthwaite (1936) has fully described the appearances found in the central nervous system.

Studies on Pathology by Other Workers

Nagayo (1923), Lewthwaite (1936) and Kouwenaar (1940) have studied the pathology of mite borne typhus.

Nagayo describes the following changes:-

The lymph glands show sinus catarrh with numerous foci of necrosis, especially in the cortex. These necroses are seen only in the glands draining the site of the eschar, and not in enlarged glands elsewhere in the body.

The spleen is usually enlarged and softer than normal. Miliary necroses are not infrequently seen in the pulp, the cells of which show proliferation. There are numerous plasma cells, large mononuclears and giant cells which are phagocytic. The liver shows cloudy swelling, and often fatty degeneration. The kidney and heart muscle show marked cloudy swelling and more or less fatty degeneration.

Lewthwaite's findings in the morbid anatomy of 12 cases correspond with what has been reported above. He also studied the histology of the brain in mite borne typhus, and found lesions in all areas, but especially in the pons and medulla, and least in the cerebellum. Rickettsiae were demonstrated in the endothelial cells of the capillaries.

Kouwenaar studied the morbid anatomy and morbid histology of the condition. His findings are comparable in most respects with those of the present author, except in certain details. Plasma cells he mentions as noticeable components of the cellular infiltrations in the various organs. In the cases reported here

they were not conspicuous. Focal necroses were often seen in the lymph glands. Apart from this, they presented the picture already described. In the kidney there was tubular degeneration but the glomeruli were intact. There were perivascular and periglomerular cellular infiltrations, but the vessels themselves were intact.

No changes were found in the gastro-intestinal tract (the present author has examined no specimens of stomach or intestines).

Conclusions

The essential lesion in mite borne typhus is vascular. Histologically this is evidenced by vascular and perivascular infiltrations of chronic inflammatory cells, and is shown by the smaller blood vessels throughout the body.

Lewthwaite (1936) has shown that *R.orientalis* is found in the lining endothelial cells of the cerebral capillaries, but the rickettsiae have not been definitely demonstrated in other organs in man. The present author attempted to demonstrate *R.orientalis* in sections of various viscera, but was unsuccessful. This was probably due to the method of fixation being unsuitable, since Fielding (1943) has obtained good results in mouse tissues, using Zenker's fixative and a modified form of Breinl's stain. Accounts of the staining of *R.prowazeki* in sections also stress the importance of using a suitable fixative, which, apparently, formalin is not. Suitable fixatives appear to those containing chromates or mercury.

Nevertheless, in view of Lewthwaite's findings in the brain, and the fact that in the other members of the typhus group of diseases the rickettsiae have always been found within endothelial cells, it seems reasonable to suppose that the same obtains in mite borne typhus in organs other than the brain.

If it is accepted, then, that *R.orientalis* is essentially an organism which invades the endothelial cells of blood vessels (and other endothelial cells, too, since it grows in the endothelium covering Descemet's membrane and in the endothelium of the mouse peritoneum) it can be seen that as a result a reactive cellular infiltration is caused around the cells containing the organisms. This is an effect secondary to rickettsial parasitism of cells and is not in itself an infiltration of specific nature, similar infiltrations, though not usually to such an extent, being seen in various subacute and chronic inflammatory states. It must be mentioned, however, that there is one point of difference between a rickettsial infiltration and an infiltration due to non-specific inflammatory causes. In the latter, an occasional eosinophil and neutrophil is always met with, but in the former condition these cells occur extremely rarely, if at all.

In the viscera this disseminated vasculitis and perivasculitis are the most prominent features. But the most important changes are those in the parenchymal cells of the organs, and these are due, it may be supposed, to the toxic effect of the rickettsiae. This is apparently the main factor concerned in

causing cellular damage in mite borne typhus, since the angeitis with thrombosis and proliferative endovasculitis seen in typhus fever are not met with.

In the myocardium, though the appearances are striking enough, there is nothing to suggest that any degree of permanent damage might result should the patient recover from the toxaemia of the actual attack of fever.

In the lungs the rickettsial vasculitis and perivasculitis produces a state of engorgement of the vessels and some desquamation of epithelial cells into the alveoli. There is also sometimes a serous exudation and there may be escape of red cells into the air spaces. Thus a state of acute pulmonary congestion is produced as a direct effect of rickettsial infection. In many respects the picture is similar to the appearances produced in primary atypical or virus pneumonia, and, in the author's view, the rickettsial condition may, in fact, be considered as a type of primary pneumonia. This condition, when uncomplicated, may produce very little in the way of clinical manifestations, as is the case in virus pneumonia (see also Section VII). But the lesion, by its very nature, is conducive to secondary bacterial infection. This always occurs in a certain proportion of cases, and is accompanied by the usual symptoms and signs of lobar or bronchopneumonic consolidation or other septic process. Nagayo (1923), Lewthwaite (1936) and Kouwenaar (1940) all note the presence of lobar or bronchopneumonic conditions, but do not mention the question of a primary rickettsial condition.

The spleen shows appearances which may be found in a variety of infective states other than mite borne typhus. The congestion, reticulo-endothelial hyperplasia and activity in the sinuses are all found in other conditions. The subintimal infiltration of the veins is also found in malaria and in chronic septic states, but, as Kouwenaar (1940) points out, it appears to be a much more prominent feature in mite borne typhus.

In the liver there are no distinctive appearances due to the rickettsial infection. The degeneration of the parenchymal cells follows the same pattern as occurs in various other infections. The portal infiltrations, too, though well-marked, are seen in other conditions.

The lesion in the kidney is interesting. It appears to be a toxic manifestation, analogous to the acute tubular nephritis which occurs in septicaemia, diphtheria and other septic states, and in chemical poisoning. The patchy distribution of the lesion in mite borne typhus, however, is in contrast to the picture of widespread tubular damage seen in other infective conditions. It appears as if certain nephrons only are unusually susceptible to the toxic effect of the rickettsial infection. The tubules of these nephrons suffer from acute degenerative changes while the tubules of adjoining nephrons undergo a process of compensatory hypertrophy, such as is seen in chronic glomerulo-nephritis. In two of the cases showing these renal lesions the clinical picture preceding death was that of uraemia. In each case the

SECTION VII

THE CLINICAL PICTURE

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THE CLINICAL PICTURE

The mite borne type of typhus is a pyrexial condition characterised by a febrile period of some two to three weeks or longer, during which certain characteristic manifestations occur. These include headache, often severe, the presence of a primary lesion or eschar, generalised enlargement of the lymphatic glands, enlargement of the spleen and liver, and the appearance of a maculo-papular rash. A flushed, and sometimes bloated, appearance of the face is often seen. This, together with a mild degree of suffusion of the conjunctivae and sometimes slight chemosis, gives the patient a characteristic appearance. Cough, usually of a slight degree, is present in a number of cases, while in some there is evidence of a more severe degree of damage to the respiratory tract.

No single one of these manifestations is to be found in every case of the disease. Indeed, cases presenting a smaller rather than a larger number of symptoms and signs are most often met with. Nevertheless diagnosis of mite borne typhus is not usually a matter of difficulty, the occurrence of certain manifestations, in small number it may be, or of a minor degree of intensity, being sufficient to suggest the diagnosis to the physician. Once suspected, recourse may be had to procedures which will offer definite confirmation.

On the other hand, cases occur which are so lacking in definite manifestations that the diagnosis becomes a matter of some difficulty if awareness of the occurrence of such cases is not kept in mind. Cases of such a type are more likely to be encountered in military rather than in civil practice, though of course they must occur in both classes of patient. Native populations in the East not infrequently dispense with skilled medical advice unless their condition is giving rise to a degree of anxiety, and even so often continue to remain in the care of the practitioner of the indigenous system of medicine. Even Europeans, resident in the East, tend to adopt self-treatment for a "touch of fever". In this way the milder forms of the disease tend to escape unnoticed. Many mild cases, too, are those in which a diagnosis on clinical grounds alone may be extremely difficult to make, though this is not always the case.

In military practice, however, illness of any type must come to the notice of the medical officer, and fevers of apparently obscure nature, quite mild it may be, and which, in the busy circumstances of general practice may well be labelled as "dengue", or "influenza", are subjected in the military hospital to full investigation.

In the following paragraphs an account is given of the manifestations of the disease, as the author has observed it in Ceylon, followed by a discussion of the diagnosis. A subsequent section deals with methods of prevention and treatment.

The clinical account is based on a study of 40

cases, accounts of which are given in the appendix to this section. All the patients were Europeans, and in each case there was a history of a stay in a known endemic mite typhus area some 10 to 14 days before the onset of symptoms.

The Incubation Period

Knowledge of endemic areas and of troop movements has enabled the incubation period in a large number of cases in Ceylon to be fixed as 10 to 14 days. This agrees with estimates given by workers in other countries.

Prodromal Manifestations

In one case (case 10) there appeared to have been prodromal symptoms, consisting of vague malaise. In the other cases, however, it has not usually been possible to determine whether or not prodromata have occurred. In a number of cases which were under observation from the very beginning of the disease no such manifestations were noted. In all cases in this series, the day on which the patient first felt ill has been taken as the first day of the disease.

The Temperature

The average duration of fever was 14 days, the extremes being 9 days and 29 days. In arriving at this estimate, cases in which complications have lengthened the duration of pyrexia have been excluded. These cases are:

Case 30, in which there was secondary pulmonary

bacterial infection and venous thrombosis.

Case 32, in which a splenic abscess developed.

Case 33, in which a complicating malarial infection obviously altered the type and duration of fever.

Case 39, in which a similar effect might have been produced by malarial infection.

Stage of invasion.

Invasion, in most cases, is quite rapid, the fastigium of fever being gained in a matter of 2 or 3 days. In most cases in this series, therefore, the period of invasion could not be observed. In those cases which were under observation from the earliest stages, different types of pyrexia at the onset were noted.

In Case 28 the temperature rose rapidly to just over 102 deg. F. in the course of 24 hours. The next day, the temperature fell to 99 deg. F. and after this commenced to rise steadily. In Case 8 the temperature was 102. deg. on admission on the 3rd. day, and thereafter remained well-elevated.

Case 1 shows another type of fever during invasion, the temperature chart having some resemblance to those seen in cases of enteric fever. There is a gradual step-like rise of temperature, the increments being of $1\frac{1}{2}$ deg. to 2 deg. F. and occurring in the evening, while there are morning remissions of about 1 deg. F.

Fastigium.

A considerable degree of variation is seen

during the height of the fever.

In many cases the pyrexia is of a continuous type, during which there may be periods of some length when there is little or no diurnal variation. This is illustrated by Case 17. In other cases the fever commences in such a fashion, but after some days the temperature begins to vary much more (Case 25). There may be well-marked daily remissions of temperature in some cases (Case 13) while in others there may be frequent intermissions (Case 11). In any case, remissions or intermissions to an extent of 3 deg. to 4 deg. F. may occur from time to time. When these occur in the first week of the disease the temperature always regains its former level within the course of the following 24 hours, but should they occur in the second week there is more likelihood of a subsequent gradual abatement of the fever.

Defervescence

The temperature falls by lysis. This may be of a comparatively rapid nature (Case 37) or, more usually, the lysis is gradual (Cases 18 and 24).

Recrudescence of pyrexia

The temperature having reached normal it is not infrequent to find a rise to 100 deg. or 101 deg. F. occurring the following day, with subsequent fall to normal within the next 24 hours. This phenomenon may be repeated again on the subsequent day (Case 25).

Recrudescences of fever of rather greater extent were seen in two cases (Cases 5 and 13). No complications were found to account for these secondary periods of pyrexia.

Rigors and Sweating

No rigors were noted in any of the cases, though about half the patients complained of chilly feelings at the onset.

Sweating occurred throughout the course of the disease in practically all the cases. Often it was profuse, especially when accompanying an intermission or marked remission of pyrexia. In Cases 3 and 37, in which sweating was profuse, a mousy odour was noted

The Facies

The general appearance was characteristic in many cases. The face was almost always flushed and sometimes presented a bloated appearance. Accompanying this, the vessels of the conjunctivae were often injected and the eyelids were slightly swollen and partially closed. The general effect, that of a rather dissipated appearance, was quite characteristic.

Pains in the Back and Limbs

Pains in the back and limbs and generalised aches occurred in rather less than half the patients and were often quite severe. Abdominal pain or discomfort was complained of by 6 patients (15%).

Headache

This was the most frequent symptom, occurring in 36 patients (90%). Frontal, occipital or generalised, it was in most cases severe, though it tended to pass off by the end of the first week. In some cases it persisted throughout the duration of the fever.

Eschar

The eschar, or primary sore, is the point of attachment of the larval mite. It is, when present in its fully developed form, a characteristic lesion. It consists of a shallow, well-demarcated ulcer $1/3$ rd. to $1/8$ th. of an inch in diameter, covered with a black crust and surrounded by a narrow zone of hyperaemia. It may be situated on any part of the body, the favourite sites being the pressure points of clothing and the natural folds. Eschars are therefore often found at the waist line, the calf at the garter area, the ankle, neck and scapular regions, and the axillae, groins and scrotum. In most cases there is only one such lesion. There may, however, be two (Cases 31 and 32).

The fully developed lesion as just described is, as Lewthwaite and Savoor (1940 b) have shown, an inconstant feature. The primary lesion, they point out, may often be an insignificant pimple which is present only in the incubation period. The lesion is at first macular, later becoming papular, and only develops to the stage of a necrotic ulcer in a few cases. Intradermal injection of monkeys with passage virus supports this view of the pathogenesis of the eschar, since in some of the animals a papular lesion which does not progress to ulceration results, while the ensuing infection may be of maximal severity

In cases in which ulceration does develop, the crust falls off about the third week and a small, well-marked crater is left. In the present series of cases eschars were present in 10 cases (25%). All the

lesions considered as eschars were well defined and conformed to the description already given. Many of the patients however, had numerous insect bites, attributed by them to ticks, leeches and mosquitoes. Owing to the impossibility of assigning to each of these lesions its true cause, those which were not "typical" in the sense already mentioned were not accounted for the purpose of arriving at the incidence of eschars, though in the light of reasons already given many of them no doubt did represent such lesions.

Glandular Enlargement

A characteristic feature of the disease is lymphadenopathy. Occurring in 30 patients (75%) it was, after headache, the most constantly present manifestation.

The cervical, axillary and inguinal glands are those most commonly affected. The occipital and epitrochlear glands may also be involved. Enlargement usually commences by the third or fourth day of fever, though sometimes it may not appear till later, and the glands are rather tender, quite mobile, firm and discrete. When an eschar is present, the glands in the lymph drainage area of the lesion may be rather larger and more tender than those in other parts of the body. The enlarged glands do not suppurate.

The Exanthem

Appearance of a rash is not a constant feature

of the condition. Noted in 17 patients (42.5%), it appeared between the 4th. and the 7th. days. Fading commences after three to four days and is usually complete within a week. There is no subsequent desquamation.

The rash is composed of discrete, dull red macules of 1 to 1.5 mm. in diameter, though somewhat larger blotchy forms are also found, and of papules which are just raised above the general skin level. It is distributed over the trunk, where its elements are usually most plentiful, and on the proximal portions of the limbs. The face, palms and soles usually remain unaffected, though this is not invariably the case. The face was affected in Case 10 and the palms and soles in Case 37.

The exanthem is not often profuse; in some cases its elements may be very scanty.

The Cardiovascular System

A feature of the disease is the relatively slow rate of the pulse as compared with the degree of the temperature. Even with a temperature of 104 deg. F. the pulse rate may not exceed 96 per minute, and though in some cases the rate may increase to 110 or 120 by the second week, it generally remains between 80 and 90 throughout the course of the disease.

The rhythm is regular, though sometimes dicrotism is well marked. The tension is usually well maintained though there may be some lowering after prolonged pyrexia.

Examination of the heart itself revealed no

abnormalities in any of the cases in this series. In 4 cases (Cases 3, 16, 31 and 40) tachycardia and palpitations occurred in convalescence and persisted for two or three weeks. The exercise tolerance of these patients was poor, but returned to normal when the pulse rate and rhythm finally settled down. No other abnormalities were detected in the cardiovascular system in these cases.

Respiratory System

Fauces.

Four patients (10%) complained of sore throat during the first week of the illness. On examination there was some slight hyperaemia of the fauces. Swabs were negative for *C.diphtheriae* (Cases 2, 8, 32 and 37).

Nares.

Epistaxis occurred in 3 cases (Cases 28, 31 and 33). It was not severe.

Bronchi.

Eleven patients (27.5%) complained of cough. This was present at the earliest stages and varied from a slight, infrequent manifestation to a more severe and painful cough which was productive of only a little sputum. In most of the cases, whether or not cough was present, no physical strains of disease were detected in the respiratory system. In two cases (Cases 1 and 37) the signs of acute bronchitis were present.

Lungs.

In 5 patients (Cases 27, 28, 29, 30 and 31)

there were signs of more extensive involvement of the respiratory tract. As has been noted in Section VI, the view is taken that the rickettsial vasculitis produces, as an effect of its own, a condition in the lungs which resembles, in some aspects, atypical or virus pneumonia.

Clinically the findings in the 5 cases mentioned above tend to confirm this view. Thus in Cases 27, 28 and 29 the physical signs in the lungs amounted to no more than those of bronchitis, and some fine crepitations on inspiration and expiration. In Case 30 there was, in addition, some impairment of the percussion note, while in Case 31 it is considered that the primary, rickettsial, condition was complicated by secondary bacterial bronchopneumonia, accompanied by its usual symptoms and signs.

Unfortunately, radiological examination was made in one case only. Dingle et al. (1944) and other workers have shown that the symptoms of primary atypical pneumonia may be very slight indeed, yet radiological evidence of the condition is present. Ahlm and Lipschutz (1944), also, have shown that in mite borne typhus there is radiological evidence of an atypical virus-like pneumonia in 20% of cases in which there are respiratory manifestations.

Alimentary System

Vomiting.

Vomiting occurred in 3 cases (7.5%). In two patients it occurred only once, at the onset. In another it was repeated once or twice.

The tongue.

The tongue was furred but moist in most cases

during the course of the first week. In the second week the fur began to disappear, persisting longest in the central area of the tongue and leaving the periphery first, so that the edges of the tongue came to have a stripped appearance.

The Abdomen.

In 5 cases (12.5%) there was complaint of abdominal discomfort. In some cases this was of a rather vague nature and of minor intensity, and no tenderness or resistance was detected on examination. In others, the discomfort was related to enlargement of the spleen.

The spleen was palpable in 19 cases (47.5%), varying from an extent of three fingerbreadths below the costal margin to just palpable enlargement. In some patients with palpable spleens there was a concurrent malarial infection. Enlargement of the spleen was detected at the third day of the disease as the earliest instance of the presence of this manifestation. In other cases, admitted to hospital between the third and tenth days, the spleen was palpable on first examination. In most cases the enlarged spleen was not tender on palpation.

The liver was palpable in 8 cases (20%). The organ was never more than slightly enlarged, extending one fingerbreadth at the most below the costal margin. There was some tenderness on palpation in 2 patients.

Disturbances of the Bowels.

Two patients (5%) had diarrhoea at the onset of their illness, which soon cleared up. A larger

number, 10 patients (25%), were constipated. This tended to be troublesome throughout the course of the disease.

Nervous System

Deafness.

Deafness to a slight degree occurred in one patient.

Dullness and apathy.

Six patients (15%) were mentally rather dull and apathetic throughout the course of the illness. This was never of a severe degree.

Delirium occurred in two patients. In both cases it occurred at night only, and was of a mild type.

Temporary paralysis of pupillary accommodation.

This phenomenon occurred in two patients towards the end of the febrile period, and lasted about a week in each case.

Urinary System

Only one patient complained of urinary symptoms. There was a burning pain on micturition during the first two to three days of his illness, which then passed off. There was no evidence of urinary infection and no abnormal constituents were found in the urine.

Haemopoietic System

Blood examinations were made in 10 cases. In most there was a slight increase in the total number

of leucocytes, though only in one case (Case 31) did this number exceed 14,000 per c.mm. This patient was suffering from bronchopneumonia.

In Case 17 there was leucopenia. The first examination performed on the 6th. day of the disease showed a normal differential count, but on the second examination 5 days later there was a relative monocytosis and a relative neutropenia.

In the remaining cases (Cases 4, 8, 11, 13, 18, 25, 27 and 32) the percentage of neutrophils was either normal, or decreased with an increase of the lymphocytes.

No red cell counts or haemoglobin estimations were made during the course of the fever. These examinations were carried out in most cases during convalescence and showed, usually, a mild degree of secondary anaemia. The blood count returned to normal in all cases by the end of convalescence.

The Weil-Felix Reaction

This was performed as described in Section V. In most cases the dilution of 1 in 320 or 1 in 640 was the last put up. In a few cases one sample of serum was examined to ascertain in how high a dilution agglutination could be obtained.

Other Examinations

In most cases a variety of laboratory examinations were carried out to exclude the possibility of the presence of diseases other than mite borne typhus. Thus in every case numerous blood films were examined

for malaria parasites, the faeces were examined for protozoa and micro-organisms where there were abdominal symptoms, the Widal reaction was performed along with the Weil-Felix reaction in many cases, throat swabs were examined where indicated, and various other procedures were carried out. The results have not been reported here, except when of special interest.

DIAGNOSIS

Early diagnosis of the mite borne type of typhus depends on a correct appreciation of the clinical features. Where several manifestations of the disease are present together, the task is not difficult. Thus adenitis with, it may be, an eschar, and continued fever presently followed by the appearance of a maculo-papular rash, would strongly suggest the nature of the condition. But, as has been seen, cases in which a sufficiency of characteristic manifestations enable the diagnosis to be arrived at readily are not always met with. In such cases the physician will not be misled if the possibility of a rickettsial causation is kept in mind when dealing with cases of pyrexia of seemingly obscure nature.

The Weil-Felix reaction gives valuable assistance in diagnosis, but as has already been seen, early positive results are not to be relied on.

Animal inoculation should be carried out when suspected sporadic cases are met with, especially when the patient comes from an area not hitherto known to be endemic, since it is of obvious importance that areas in which the disease occurs should be mapped.

ed out.

DIFFERENTIAL DIAGNOSIS

Malaria.

Malaria is always the first consideration to be dealt with. Exclusion of malarial infection depends on the absence, on repeated test, of malaria parasites in the blood, but the presence of parasites does not exclude mite borne typhus. The two diseases not infrequently co-exist, since in endemic mite borne typhus areas the principal disease is usually malaria and not mite borne typhus. Absence of response to anti-malarial treatment indicates that such an infection is not the sole condition present.

Dengue.

This disease is often very similar to mite borne typhus in its initial stages. Thus in dengue there is also flushing of the face, injection of the conjunctivae, severe headache and generalised pains, and there may also be generalised glandular enlargement, though this is usually of lesser degree than is the case in mite borne typhus. The "saddle back" form of temperature chart in dengue may be of some assistance if the intermission lasts more than 48 hours. Should this be the case, the presence of mite borne typhus is unlikely. But many dengue cases show only a short remission, or none at all. The rash, if it occurs, may help. It is not dissimilar to that of mite borne typhus, but it tends to occur first, and most well-marked, on the distal portions of the limbs.

In a number of cases, however, it may not be possible to make a definite diagnosis till the 6th. or 7th. day, by which time the temperature returns to normal in all cases of dengue.

The enteric fevers.

The onset of mite borne typhus is much more rapid than is the case in typhoid fever. A patient with mite borne typhus at the end of the first week may be as ill as a patient at the end of the third week of typhoid fever. Intestinal symptoms are little marked in mite borne typhus, while glandular enlargement and the presence of an eschar do not occur in enteric. The rash in enteric is usually of later appearance than is the case in mite borne typhus. The greatest difficulty arises in differentiating cases of mite borne typhus in which the characteristic manifestations are not prominent from enteric fever occurring in inoculated persons. In these latter cases, pyrexia with a little abdominal discomfort is sometimes all that is to be found. Similar difficulties may occur in the case of the paratyphoid fevers, especially as these diseases are of more rapid onset than is the case in typhoid fever.

In all cases, the results of blood culture, culture of the urine and faeces, and the appropriate agglutination reactions are of great assistance.

Measles.

Mite borne typhus, at its onset, may be mistaken for measles when dealing with children or light-skinned Asiatics. The reverse is not likely to occur. The course of the disease makes the diagnosis clear.

Primary bronchitis and bronchopneumonia.

Where respiratory manifestations are prominent the true nature of the infection may be overlooked unless careful examination be carried out.

Meningitis.

Though no difficulty arose in this connection with the cases here described, stiffness of the neck has been found in some series of cases. In mite borne typhus the cerebrospinal fluid may sometimes be under increased pressure, and there may be an increase in protein to 100 mgm.%. Cell counts of up to 80 lymphocytes per c.mm. have also been recorded.

Septic sores and lymphadenitis.

An eschar and the accompanying lymphadenitis may be mistaken for an ordinary septic process. Such manifestations, in the tropics, should cause suspicion of mite borne typhus and lead to a search for confirmatory signs.

Glandular fever.

This is a not uncommon diagnosis in the initial stages of the disease, and is usually made in areas where the presence of mite borne typhus is not suspected. The course of the illness and blood examination enable the correct diagnosis to be made, and the appropriate agglutination tests are of value.

Bubonic plague.

The atypical varieties of plague, and the milder forms, may cause difficulty, but such types usually occur during the course of an epidemic, in which case the possibility of plague would already be in mind.

Leptospirosis.

In the initial stages, leptospirosis without

jaundice may have to be differentiated from mite borne typhus. The muscular pains are generally much more severe than are the aches and pains of the latter condition. The haemorrhagic features of leptospirosis are also a valuable diagnostic manifestation.

Other members of the typhus group of fevers.

Differentiation of mite borne typhus from the other members of the group is not usually a difficult matter. Firstly, it is essential to differentiate the disease from louse borne typhus, since from the point of view of the public health as well as from the patient's own outlook, the two conditions vary so much.

Louse borne typhus is a much more severe disease than is mite borne typhus, and nervous manifestations, delirium or apathy, are prominent features. The exanthem is also better marked than is that of mite borne typhus, and may be petechial or frankly haemorrhagic. There is no eschar, though louse bites and excoriations from scratching may be present, and there is no lymphadenopathy. As with many other conditions, as already noted, the difficulty arises when mild forms of louse borne typhus are met with. The Weil-Felix reaction and other laboratory tests are then of great value. It may be mentioned, also, that louse borne typhus is very uncommon in those areas in which the mite borne type occurs. This is due to the relatively low incidence of body louse infestation in the tropics.

There is a little more difficulty in differentiating mite borne typhus from the tick borne variety. Both occur in the same areas, in India, though the

presence of these two types of typhus-like disease in the same country, or locality has not been reported from elsewhere. In the tick borne type the rash is usually prominent and may be petechial, while in the mite borne type it is never very prominent, is almost never petechial, and may be absent. There is no adenitis in the tick borne type, and no true eschar.

The flea borne type of typhus is of world-wide occurrence. It is always a mild disease, and a rash may or may not be present. There is no eschar or lymphadenitis. The disease is essentially urban in its occurrence.

The Weil-Felix reaction is of the greatest value in differentiating typhus of the mite borne type from other diseases of the group, since the agglutination reactions are clear cut. Differentiation of the remaining members of the typhus group from each other is a matter of more difficulty, which need not be dealt with here.

Mite Borne Typhus in Other Countries

In Table 9 a summary is given of recent reports on the clinical aspect of mite borne typhus from Malaya, Australia, the South West Pacific area and Japan. The figures from the present series of cases are included for comparison.

Conclusions

Mite borne typhus is an acute infective disease in which, as a result of parasitism of endothelial cells throughout the body by *R.orientalis*, certain pathological effects are produced. Clinically, these

Table 9

Symptom	Ceylon 40 cases	Malaya 250 cases Lewthwaite and Savoor (1940 b)	Australia 54 cases Heaslip (1941)	S.W.Pacific 70 cases Ahlm and Lipschutz (1944)	Japan Nagayo (1923)
Headache	90	92	Most cases	Majority of cases	Most cases
Muscular pains	45	2	Most cases	Most cases	Most cases
Abdominal dis- comfort	15	3	0.5	60% had abdominal discomfort with nausea and vomiting	Sometimes
Constipation	25				Often
Diarrhoea	5	34		Occasional	Quite common
Vomiting	7.5	39	Sometimes		Occasional
Deafness	2.5	66		34	Very frequent
Epistaxis	7.5	1.5			
Cough	27.5	Catarrh, 28%; Rales & rhonchi 64%; broncho- pneumonia 13%	Bronchitis freq- uent; pneumonia occasional	67% had cough: 20% of these had an atypical pneumonia	Bronchitis & bronchopneu- monia some-
lry. pneumonia	10				
2ry. pneumonia	2.5				
Sore throat	10		Sometimes		
Injection of conjunctivae	45	40	Variable	Most cases, appar- ently	May be present
Eschar	25		35	67	Constant
Rash	42.5	All Europeans & most Sikhs	61.5	91	Apparently all cases
Lymphadenopathy	75	40	Variable	94.5	Constant
Splenomegaly	52.5	80	25		Most cases
Hepatomegaly	22.5		Variable		Many cases
Mental changes	17.5	In grave cases		Delirium if severe	If severe
Mortality rate	Very low	15-30	2	1 case fatal	30

Note. Figures represent percentages

are evidenced by symptoms and signs, some of which are due to the fever and toxæmia generally, while others are to be directly attributed to the rickettsial lesion.

Among the manifestations due to toxæmia may be included headache, generalised aches and pains and probably disturbances of the bowels. Due specifically to the rickettsial lesion are the rash, eschar, lymphadenopathy, pulmonary congestion and mental changes. Splenomegaly and hepatomegaly are also probably due to the presence of rickettsial lesions in these organs. The heart, too, is affected, but in most cases the only clinical evidence is a comparative bradycardia. Sometimes tachycardia is present and there may be palpitations.

The relative frequency of the symptoms and signs varies in different countries. This is probably due to differences in the strains of *R.orientalis* concerned. The disease is of an essentially focal nature. That is to say, it occurs in delimited areas often quite widely separated from each other. In fact, many of the foci are islands. Thus it can be envisaged that each focus of infection has its own rickettsial strain, and that these strains do not tend to become disseminated far afield from their place of origin. Such a conception is supported by the facts known with regard to the epidemiology of the disease. Thus rats appear to suffer from a short-lived rickettsial infection only, and therefore any tendency to dissemination of rickettsial strains by the migrations of these rodents is minimal. Further more, infection of man represents

for the infecting rickettsiae the end of their life cycle. Whatever the outcome of the case, should the patient recover or should he die, the rickettsiae within his body have ended their biological existence. They cannot be transmitted to other human beings or to lower animals or insects.

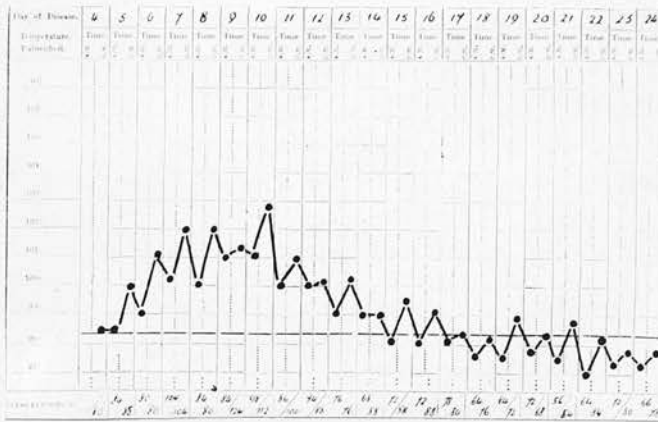
In this way, it can be considered that a number of "pure strains" of *R.orientalis* exist in the various foci of infection. All strains produce the same disease, but the details, as it were, vary.

Some remarks on immunological relationships between various strains of *R.orientalis* may be made in this context. As has been mentioned in Section 111, all strains of *R.orientalis* so far tested have proved to be immunologically identical. But the method of testing - by cross-immunity experiments on animals - is comparatively crude. Though reciprocal tests in animals might show that any two or more strains could immunise each against the others, it is open to question whether comparatively small variations in antigenic structure do not escape detection by such methods. It may be found that when more sensitive methods of antigenic estimation are elaborated, such as agglutinin absorption and other tests, variations in clinical manifestations are correlated to antigenic differences in the causal organisms.

APPENDIX TO SECTION VII

The cases have been arranged in such a manner as to present first those which are the most typical examples of the disease. As the series progresses the cases deviate from the usual pattern. It will be seen that this is more from a lack of characteristic manifestations than from the presentation of any unusual features. Cases 1 to 26 form this part of the series.

Cases 27 to 31 are those in which respiratory manifestations were prominent. Case 32 was complicated by the development of a splenic abscess. Cases 33 to 40 were complicated by malaria.

CASE 1

This is a typical case of mite borne typhus. The patient showed most of the characteristic manifestations of the disease, which was of a moderate degree of intensity.

The patient complained of severe headache, mainly frontal, backache and pains in the limbs. There was also some looseness of the bowels and a slight cough. The symptoms were of 4 days duration.

On examination, the patient presented a characteristic appearance, with flushed face, suffusion of the conjunctivae and some wateriness of the eyes. An eschar was present on the back, between the angles of the scapulae. The right axillary glands were enlarged, firm and slightly tender, but at this stage neither the liver nor the spleen were palpable. Examination of the respiratory system showed the cough to be due to a mild degree of bronchitis.

The temperature continued to rise till the 7th. day of the illness, with evening increments of about 1.5 deg. F. and morning remissions. During this period the liver and spleen both became palpable, extending to just below the costal margin, and in addition, the

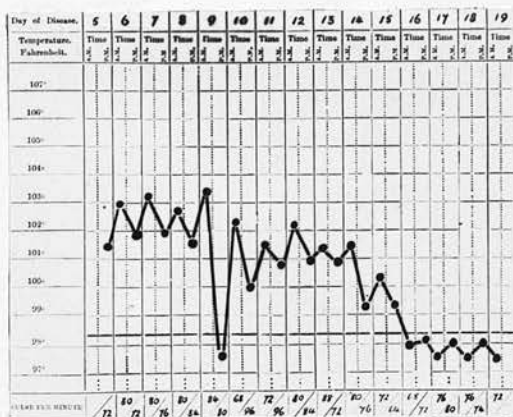
left axillary, the cervical and the inguinal glands enlarged.

On the 7th. day the rash appeared. Dull red macules and papules were distributed fairly profusely on the trunk and proximal portions of the limbs, the face and distal parts of the extremities escaping. By the 9th. day the exanthem had faded to a considerable degree, and by the 11th. day had entirely disappeared. During the period in which the rash was visible the temperature maintained a level of 101 deg. to 102 deg. F. with little diurnal variation, while from the 11th. to the 16th. day it fell by lysis. The pulse rate remained low in relation to the temperature level throughout the course of the disease.

During the height of the pyrexia the cough became slightly more marked, but apart from the general discomfort there were no other symptoms. The mental functions remained clear throughout. With the fall in the temperature the symptoms rapidly ameliorated. Convalescence was uneventful.

Weil-Felix reaction:

	6th. day	14th. day
Proteus OXX	1/80	1/320
Proteus OX19	0	0
Proteus OX2	0	0

CASE 2

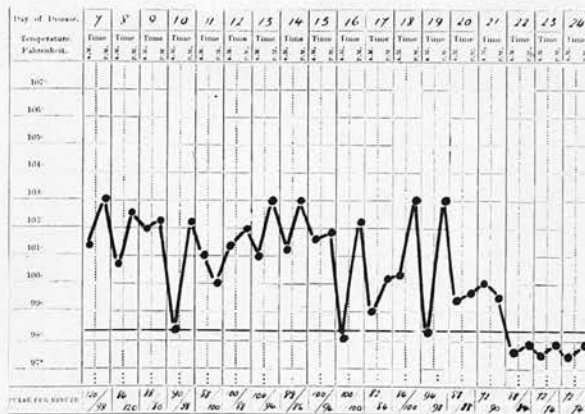
This patient was admitted to hospital on the 5th. day of the disease. He complained of headache, feverishness and slight sore throat.

On examination, the face was flushed and appeared bloated. The conjunctivae were suffused. An eschar was present on the anterior fold of the right axilla and the right axillary glands were enlarged and slightly tender. The spleen was enlarged, extending one fingerbreadth below the costal margin.

On the 7th. day a characteristic maculo-papular rash appeared on the trunk and proximal portions of the limbs. The left axillary and the cervical and inguinal glands were now also enlarged. No further manifestations appeared, and by the 14th. day deferescence had commenced. Convalescence followed uneventfully.

Weil-Felix reaction:

	8th. day	18th. day	30th. day
Proteus OXK	0	1/320	1/10,240
Proteus OX19	0	0	0
Proteus OX2	0	0	0

CASE 3

This patient complained of feverishness and headache of 7 days duration.

A maculo-papular rash was present on the trunk and thighs, on admission. It persisted for 3 days. The cervical and inguinal glands were enlarged and the liver and spleen were both palpable one finger-breadth below the costal margin. No eschar was found.

During the course of the fever there was much sweating. This was associated with a peculiar mousy odour, which persisted for about a week. No complications developed but by the end of the fever the patient was quite exhausted. During convalescence there was tachycardia, and occasionally palpitations.

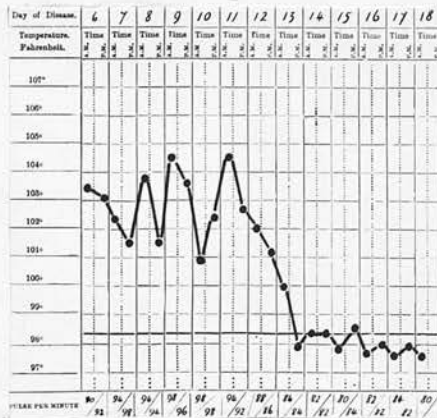
Weil-Felix reaction:

10th. day

Proteus OXK 1/160

Proteus OX19 0

Proteus OX2 0

CASE 4

The patient was admitted on the 6th. day of illness, complaining of feverishness and headache. A macular rash was present on the trunk, upper arms and thighs, and the face showed a rather blotchy erythema. An eschar was present on the outer aspect of the right ankle and the axillary glands were enlarged, firm and slightly tender.

Pyrexia lasted for 13 days, and the patient made a rapid recovery.

Weil-Felix reaction:

9th. day

Proteus OXK 1/320

Proteus OX19 0

Proteus OX2 0

Blood examination:

8th. day

W.b.c. : 10,000

Neutrophils: 34%

Eosinophils: 1%

Lymphocytes: 60%

Monocytes : 5%

14th. day

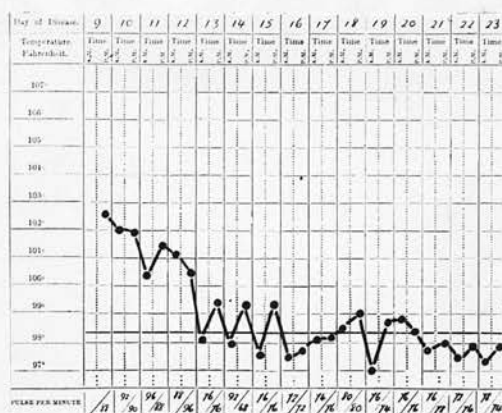
12,400

48%

5%

42%

5%

CASE 5

This is a typical case of mite borne typhus of a mild type.

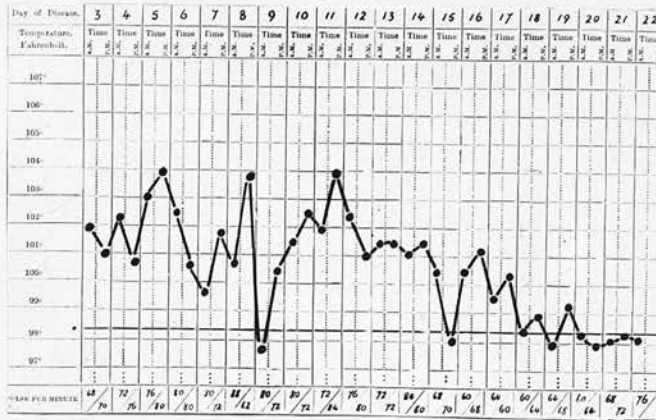
The patient was admitted on the 9th. day, complaining of headache, aching of the eyes, pains in the elbows and shoulders, loss of appetite and constipation.

On examination, a rash consisting of dull red macules was seen on the trunk. The spleen was just palpable and the axillary and inguinal glands were enlarged. The liver was not palpable and no eschar was seen.

Two days after admission the rash was much less marked, and in another two days it had disappeared entirely. After the main pyrexial period, which lasted for 15 days, there was a slight recrudescence of fever of 3 days duration.

Weil-Felix reaction:

	15th. day	30th. day
Proteus OXK	1/320	1/640
Proteus OX19	0	0
Proteus OX2	0	0

CASE 6

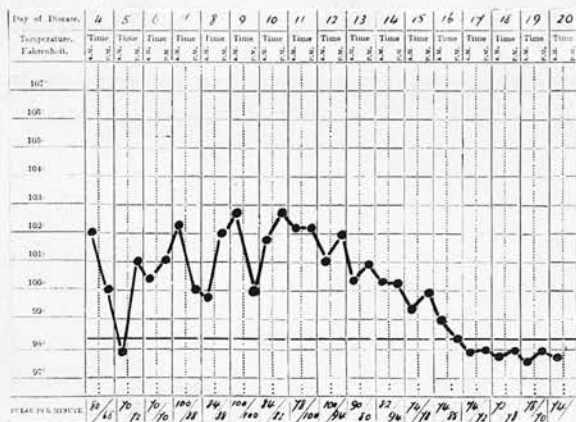
This is another example of a typical attack of mite borne typhus, though the rash was absent. The patient was admitted on the 3rd. day, complaining of severe headache.

On examination, the face was flushed and the conjunctivae were suffused. An eschar was present on the right side of the neck, just above the clavicle. The occipital, cervical, axillary, epitrochlear and inguinal glands were enlarged, and the liver and spleen were both just palpable.

On the 12th. day the patient complained of pain in the region of the spleen, which now extended two fingerbreadths below the costal margin and was tender on palpation. Two days later, however, the discomfort had much diminished and the spleen was beginning to diminish in size. This coincided with a fall in the temperature, but defervescence did not commence till the 16th. day. Recovery ensued without complication.

Weil-Felix reaction:

	9th. day	17th. day
Proteus OXK	1/40	1/320
Proteus OX19	0	0
Proteus OX2	0	0

CASE 7

This is a case of moderate severity in which no eschar was found and there was no palpable enlargement of the liver or spleen.

The patient was admitted on the 4th. day, complaining of headache, pains in the back and limbs and nausea. Vomiting had occurred twice. The face was flushed and the conjunctivae were injected. A rather scanty macular rash was present on the chest. The cervical and inguinal glands were enlarged.

Severe headache persisted till the 12th. day, when lumbar puncture was performed. The C.S.F. was under slightly increased pressure, but was clear. The fever followed a course of 16 days, during which there were no complications. Recovery was uninterrupted.

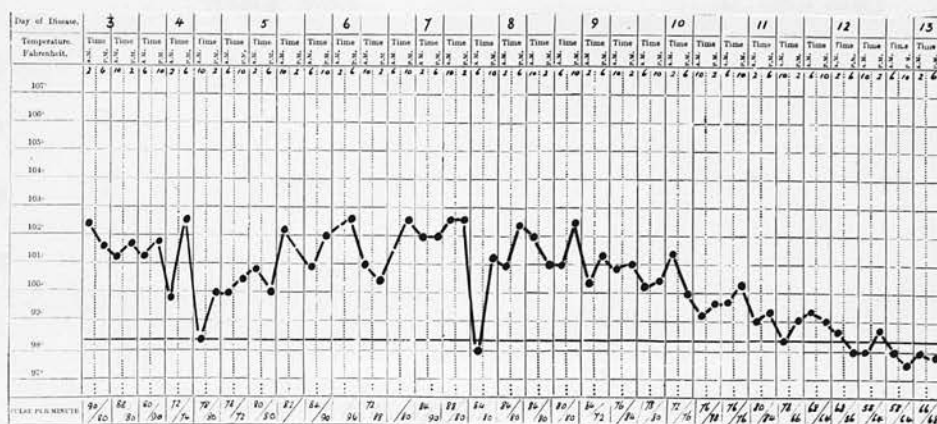
Weil-Felix reaction:

18th. day

Proteus OXK 1/640

Proteus OX19 0

Proteus OX2 0

CASE 8

The patient complained of severe headache, abdominal discomfort and constipation, of 2 days duration. There were also generalised aches and pains, and a slight cough was present.

On examination, there was little abnormal at this stage, apart from the presence of fever, and an eschar, which was situated on the inner side of the right arm.

The rash, typical in appearance, appeared on the 5th. day. It involved the face, neck, trunk and upper extremities, and began to fade 3 days later. There was slight abdominal tenderness, rather vague in character, and not localised to any particular area. Neither the liver nor the spleen were palpable. There was no lymphadenopathy. There were no abnormalities in the respiratory system, apart from the slight cough.

The fever lasted for 12 days. There were no complications and convalescence was uneventful.

Weil-Felix reaction:

	8th. day	14th. day
Proteus OXK	1/20	1/320
Proteus OX19	0	0
Proteus OX2	0	0

Blood examination:

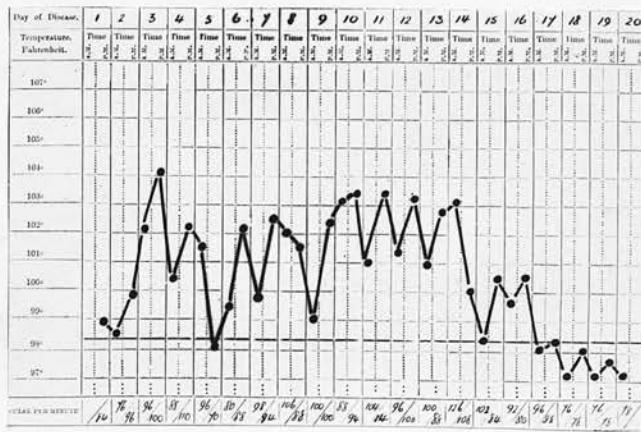
	5th. day	10th. day
W.b.c. :	9,400	5,400
Neutrophils:	70%	60%
Eosinophils:	4%	6%
Lymphocytes:	18%	26%
Monocytes :	8%	8%

CASE 9

This patient was not seen till the 16th. day of the disease. He gave a history of headache and feverishness , and of a rash which had appeared on the 4th. day and had persisted till the 8th. Even at this stage he showed a flushed appearance with suffusion of the conjunctivae. There was no eschar and the liver and spleen were not palpable. The inguinal glands were enlarged.

Weil-Felix reaction:

	18th. day
Proteus OXK	1/320
Proteus OX19	0
Proteus OX2	0

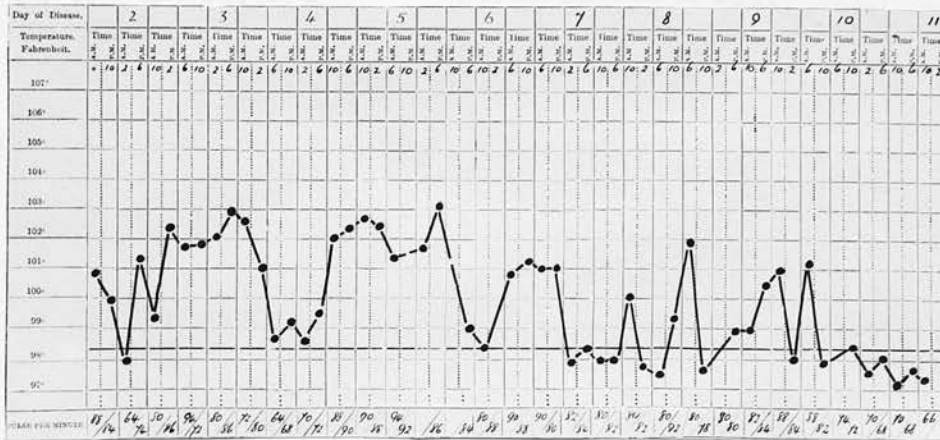
CASE 10

In this case there appeared to be a definite prodromal period of 2 days, during which the patient felt vaguely out of sorts, but with no pyrexia. When fever commenced, on the day of admission to hospital, severe headache made its appearance.

On examination, the face was slightly flushed and the conjunctivae were injected and watery. A macular rash was present on the chest; the patient had had this for some days and attributed it to sweating. On the 3rd. day the cervical, axillary and inguinal glands were found to be enlarged. On the 5th. day a typical mite borne typhus rash appeared, and persisted for 4 days. At the same time the spleen had become palpable one fingerbreadth below the costal margin, and was tender. The liver did not become palpable and no eschar was seen. Constipation was very troublesome. After quite a sharp attack of the disease, the temperature returned to normal on the 17th. day. There were no complications.

Weil-Felix reaction:

	5th. day	11th. day	18th. day
Proteus OXK	1/20	1/320	1/2,560
Proteus OX19	0	0	0
Proteus OX2	0	0	0

CASE 11

In this case the rash was the only objective manifestation, apart from fever.

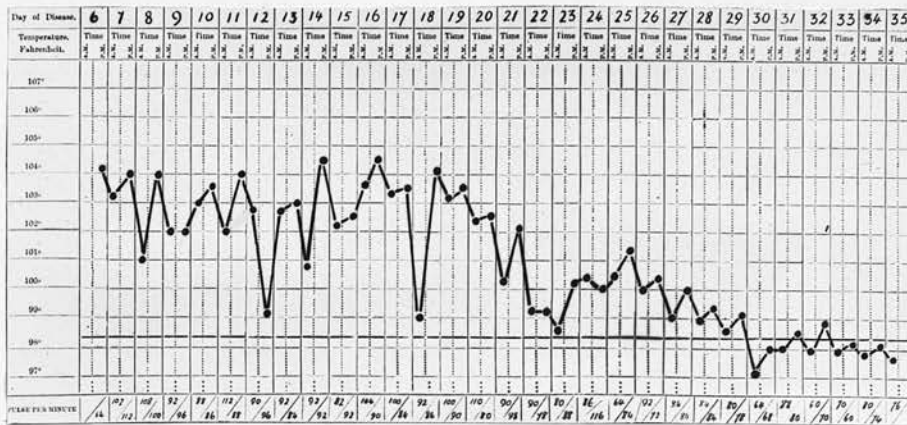
On admission the patient had had fever and constipation for 2 days. He also complained of headache, though this was not very severe, and of generalised aches and pains.

On examination, the face was flushed and the temperature was 100.8 deg. F. The pulse was relatively slow. No other abnormalities were found. On the 3rd. day of fever a maculo-papular rash appeared on the trunk. This persisted for 6 days.

Apart from these findings, the fever ran its course without any further objective or subjective manifestations. Convalescence was slow but uneventful.

Weil-Felix reaction:

	8th. day	14th. day
Proteus OXK	0	1/320
Proteus OX19	0	0
Proteus OX2	0	0

CASE 13

This patient was admitted on the 6th. day, complaining of severe headache. The face was flushed and the conjunctivae were suffused. The temperature was 103 deg. F. No other abnormalities were found. By the 8th. day the liver had become palpable one finger-breadth below the costal margin and by the 11th. day the cervical and axillary glands were enlarged. There was no eschar, a rash did not appear, and the spleen never became palpable.

Lysis appeared to be commencing on the 19th. day, but on the 23rd. day there was a recrudescence of fever. No complication was found to account for this phenomenon. When the fever finally settled, convalescence ensued uneventfully.

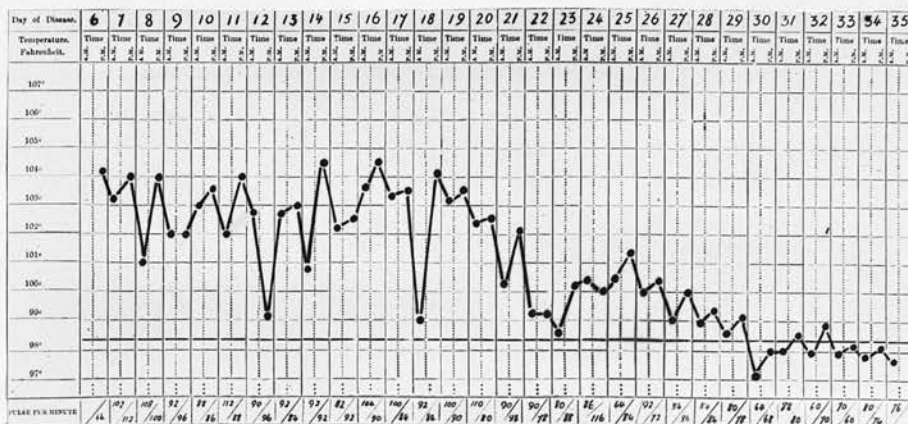
Weil-Felix reaction:

	10th. day	16th. day
Proteus OXK	1/40	1/320
Proteus OX19	0	0
Proteus OX2	0	0

Blood examination: 8th. day

W.b.c. 5,800

Neutrophils:	65%	Lymphocytes:	25%
Basophils :	1%	Monocytes :	9%

CASE 13

This patient was admitted on the 6th. day, complaining of severe headache. The face was flushed and the conjunctivae were suffused. The temperature was 103 deg. F. No other abnormalities were found. By the 8th. day the liver had become palpable one finger-breadth below the costal margin and by the 11th. day the cervical and axillary glands were enlarged. There was no eschar, a rash did not appear, and the spleen never became palpable.

Lysis appeared to be commencing on the 19th. day, but on the 23rd. day there was a recrudescence of fever. No complication was found to account for this phenomenon. When the fever finally settled, convalescence ensued uneventfully.

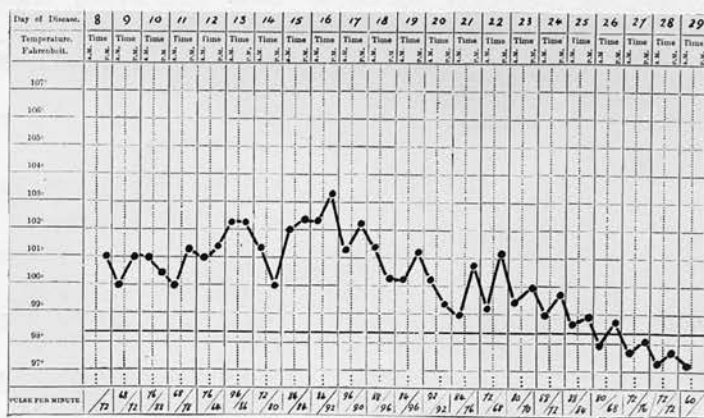
Weil-Felix reaction:

	10th. day	16th. day
Proteus OXK	1/40	1/320
Proteus OX19	0	0
Proteus OX2	0	0

Blood examination: 8th. day

W.b.c. 5,800

Neutrophils:	65%	Lymphocytes:	25%
Basophils :	1%	Monocytes :	9%

CASE 14

This patient was admitted on the 8th. day, complaining of pain shooting down the legs and headache.

On examination, the positive findings were enlargement of the spleen, which was palpable 2 finger-breadths below the costal margin, and enlargement of the cervical and inguinal glands.

By the 14th. day the spleen had diminished in size, being only just palpable. The axillary glands, however, had now enlarged. During the next 5 days the patient's condition remained more or less unchanged, the pyrexia being of a continuous type with small remissions. On the 19th. day there was complaint of pain on taking a moderately deep breath, in the region of the spleen. The spleen was not palpable, and no abnormalities were found in the respiratory system. Defervescence commenced 2 days later, the pain by now having disappeared. Convalescence was rather prolonged, owing to general debility.

Weil-Felix reaction:

	13th. day	26th. day
Proteus OXK	1/80	1/320
Proteus OX19	0	0
Proteus OX2	0	0

CASE 15

This patient had a mild attack of the disease. He was admitted on the 4th. day, complaining of headache and generalised pains in the body, though neither of these symptoms were of marked degree. The spleen and liver were both just palpable and the inguinal glands on both sides were slightly enlarged. No other abnormalities were found. Defervescence commenced on the 10th. day.

Weil-Felix reaction:

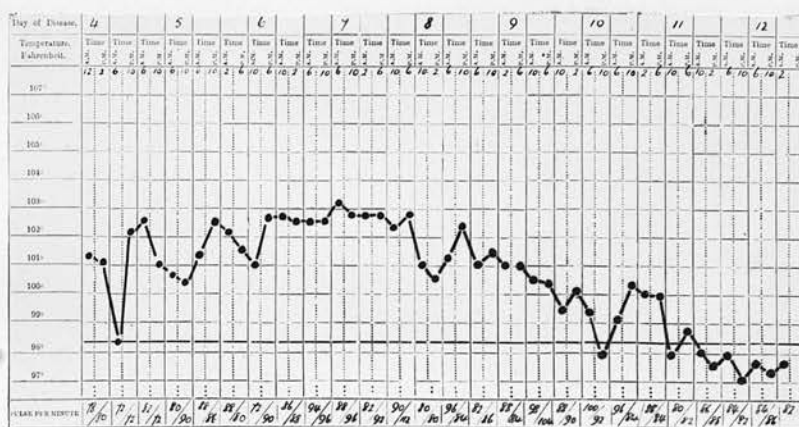
	8th. day	14th. day
Proteus OXK	1/20	1/160
Proteus OX19	0	0
Proteus OX2	0	0

CASE 16

Admitted on the 8th. day, the patient complained of headache. The only positive finding was slight splenic enlargement. Pyrexia lasted for 19 days, and during convalescence there was some degree of tachycardia and a diminished exercise tolerance. These manifestations disappeared after a fortnight's recuperation.

Weil-Felix reaction:

	12th. day	18th. day
Proteus OXK	1/20	1/640
Proteus OX19	0	0
Proteus OX2	0	0

CASE 17

The patient complained of severe headache, pains and aches all over the body and feverishness, of 4 days duration. There was also constipation.

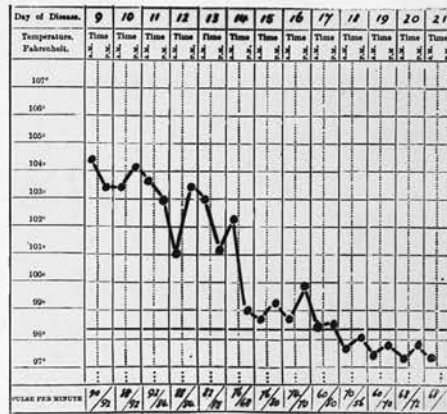
There were few objective manifestations. The patient had a slight cough, and vomited twice on the 6th. day. There was no rash or eschar, or enlargement of the lymphatic glands, liver or spleen. The patient made a good recovery, though convalescence was prolonged owing to general debility.

Weil-Felix reaction:

	7th. day	12th. day
Proteus OXK	1/80	1/320
Proteus OX19	0	0
Proteus OX2	0	0

Blood examination:

	6th. day	11th. day
W.b.c.	4,000	3,200
Neutrophils:	66%	50%
Eosinophils:	2%	4%
Lymphocytes:	28%	30%
Monocytes :	4%	16%

CASE 18

The patient was admitted on the 9th. day. He made no complaint other than that he felt a little unwell.

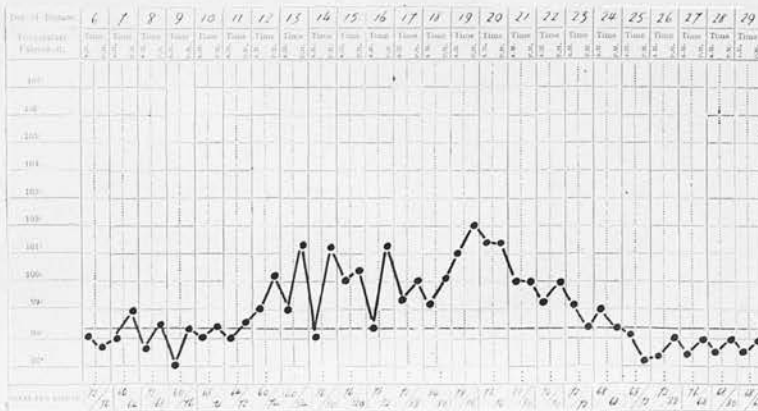
On examination, he was found to be rather dull, mentally. The cervical, axillary and inguinal glands were enlarged, and the liver and spleen were both just palpable. Between the 8th. and the 10th. days the patient was slightly at night, but there were no other complications. After defervescence recovery was rapid.

Weil-Felix reaction:

	10th. day	17th. day
Proteus OXK	1/160	1/320
Proteus OX19	0	0
Proteus OX2	0	0

Blood examination:

	10th. day	16th. day
W.b.c.	10,000	11,400
Neutrophils:	56%	64%
Eosinophils:	-	3%
Basophils :	-	1%
Lymphocytes:	41%	28%
Monocytes :	3%	4%

CASE 19

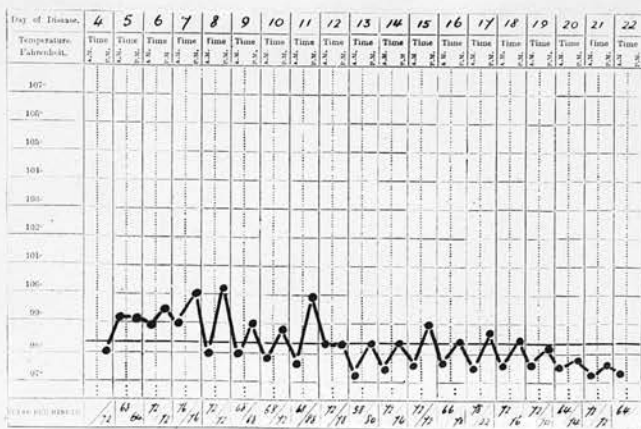
This patient was admitted to hospital for treatment of malaria. At the same time he was in the incubation period of mite borne typhus.

He had first felt ill 6 days prior to admission. Benign tertian malaria was diagnosed and the patient was evacuated to hospital for completion of treatment. On the 7th. day after admission to hospital the temperature, which had up till now been normal, began to rise and the patient complained of headache. Blood films examined during the course of the next few days showed no malaria parasites. On the 3rd. day of fever the spleen was palpable one fingerbreadth below the costal margin, and the right inguinal glands were slightly enlarged. The fever progressed as shown on the chart, no fresh symptoms or signs presented themselves, there were no complications and convalescence followed uneventfully.

Weil-Felix reaction:

8th. day

Proteus OXK 1/640
 Proteus OX19 0
 Proteus OX2 0

CASE 20

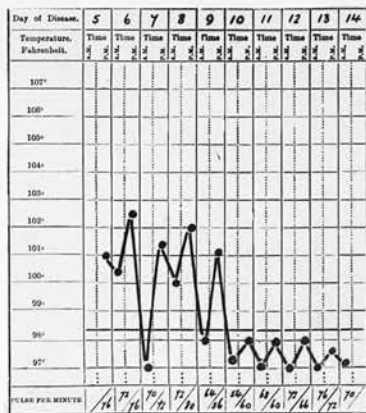
This patient was admitted to hospital with a history of diarrhoea of 4 days duration. No abnormalities were found on physical examination.

On the 2nd. day in hospital the temperature began to rise. During the course of the ensuing fever the stools, of which there were about two a day, and quite well formed, were examined several times. No amoebae or cysts were found and no organisms of the enteric-dysentery group were isolated on culture. Repeated blood films showed no malaria parasites. The only physical sign discovered was slight enlargement of the axillary glands of both sides, which appeared on the 5th. day.

The patient was little affected by the mild degree of fever, and on defervescence full recovery was rapid.

Weil-Felix reaction:

	4th. day	10th. day
Proteus OXK	1/20	1/320
Proteus OX19	0	0
Proteus OX2	0	0

CASE 21

The temperature chart in this case conforms more to the usual pattern seen in mite borne typhus than was the case with the previous patient. The pyrexial period was short.

The patient was admitted on the 5th. day of the fever. His only symptoms were those associated with an elevated temperature, and no physical signs of disease, apart from pyrexia, were discovered.

Weil-Felix reaction:

	10th. day	19th. day
Proteus OXK	1/640	1/2,560
Proteus OX19	0	0
Proteus OX2	0	0

CASE 22

This patient was admitted to hospital on the 5th. day of his illness. He complained of headache only.

On examination, his face was rather flushed and his conjunctivae were suffused. No other symptoms or signs were noted. The temperature continued between 100 deg. and 101 deg. F. for a further 5 days, when it descended by lysis. The patient made a rapid recovery.

Weil-Felix reaction:

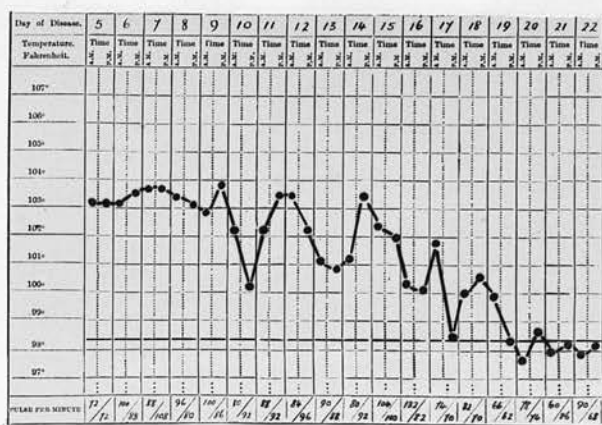
	8th. day	16th. day
Proteus OXK	1/20	1/320
Proteus OX19	1/20	1/20
Proteus OX2	0	0

CASE 23

This patient was admitted on the 7th. day, complaining of headache. The characteristic flushing of the face with suffusion of the conjunctivae were present, but there was no rash or eschar and the liver and spleen were not palpable. There was slight enlargement of the axillary and inguinal glands. Pyrexia lasted for 12 days. There were no complications.

Weil-Felix reaction:

	10th. day
Proteus OXK	1/320
Proteus OX19	0
Proteus OX2	0

CASE 25

The patient was admitted on the 5th. day, complaining of headache.

On examination, the face was flushed and the conjunctivae were suffused. There was no rash or eschar, the liver and spleen were not palpable and there was no enlargement of the lymphatic glands. The patient was drowsy and apathetic throughout the course of the disease, but there were no complications. After defervescence, recovery was rapid.

Weil-Felix reaction:

11th. day

Proteus OXK 1/640

Proteus OX19 0

Proteus OX2 0

Blood examination:

10th. day

W.b.c. : 8,000

Neutrophils: 71%

Eosinophils: -

Basophils : 1%

Lymphocytes: 26%

Monocytes : 2%

17th. day

10,800

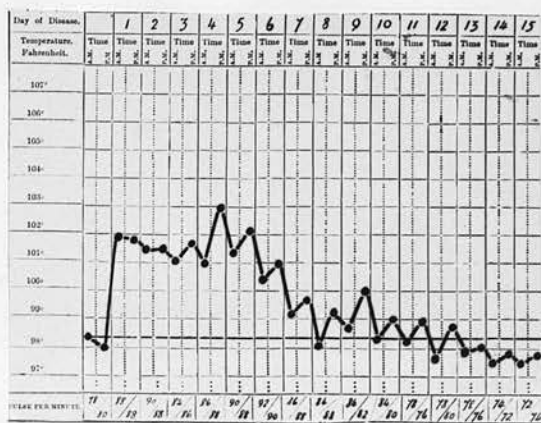
49%

2%

-

43%

7%

CASE 26

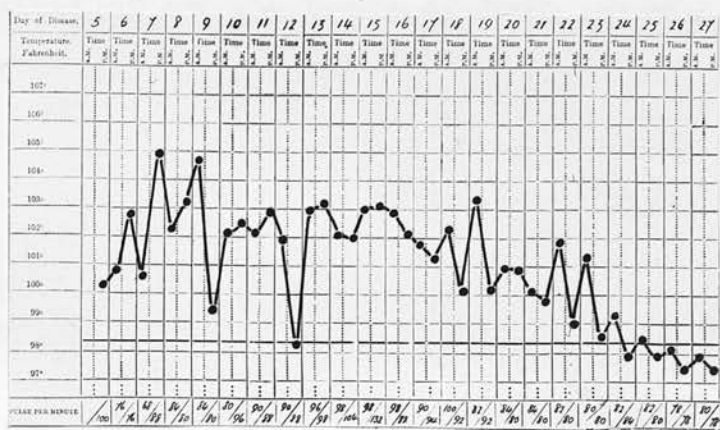
This is another example of a patient who was admitted to hospital while in the incubation period of mite borne typhus.

The patient was admitted for treatment of chronic otitis media. On the second day in hospital the temperature rose to 102 deg. F., and remained elevated for 12 days. No malaria parasites were found in the blood. Apart from enlargement of the cervical glands there were no other symptoms or signs. The patient had just come from a known endemic area of mite borne typhus.

The course of the disease was very mild, and the patient made a rapid recovery.

Weil-Felix reaction:

	6th. day	18th. day
Proteus OXK	1/80	1/640
Proteus OX19	0	0
Proteus OX2	0	0

CASE 27

The patient complained of headache and pain behind the eyes, feverishness and constipation, of 5 days duration.

On examination, the face was flushed but there was no suffusion of the conjunctivae. A rash was present, consisting of a few pale red macules, on the thorax, and a blotchy erythema was seen on the abdomen and upper arms. An eschar was present on the suprapubic region and the cervical, axillary and inguinal glands were enlarged. The liver and spleen were not palpable.

An irritating cough with scanty sputum was present and scattered rhonchi could be heard in all areas in both lungs. There were no changes in vocal fremitus or resonance, or in lung resonance or in the breath sounds.

Up till the 13th. day the pyrexia continued to be of a swinging type, but thereafter little diurnal variation was noted. By the 17th. day it seemed as if lysis had commenced. On the 18th. and 19th. days, however, there was a recrudescence of pyrexia to a higher degree and the cough became more marked. Examination showed an increase in the respiratory rate,

and the presence of fine crepitations on inspiration and expiration at the bases of both lungs. Movement was undiminished, vocal fremitus and resonance were unaltered, there were no changes in the percussion note, and the breath sounds were vesicular. In the course of the following two days lysis commenced, with disappearance of the basal crepitations and decrease of the respiratory rate.

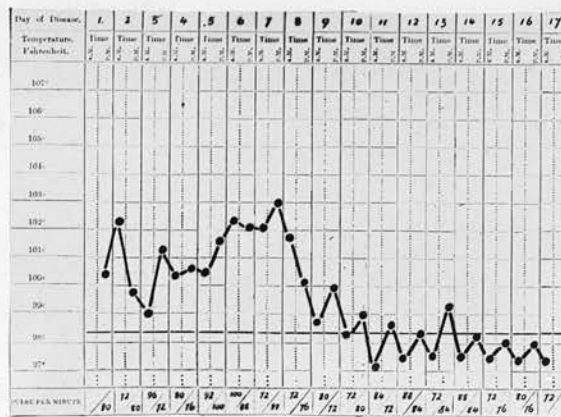
Headache had meanwhile been very troublesome. On the 20th. day lumbar puncture was performed, clear C.S.F. under slightly increased pressure being withdrawn. The headache was completely relieved. On the 18th. day a slight degree of deafness had developed and there was some confusion with a mild degree of delirium at night. Also, there was loss of pupillary accomodation. These phenomena persisted till defervescence was complete. Convalescence was uneventful.

Weil-Felix reaction:

	10th. day	15th. day	22nd. day
Proteus OXK	1/20	1/320	1/20,480
Proteus OX19	0	0	0
Proteus OX2	0	0	0

Blood examination:

	6th. day	16th. day
W.b.c. :	4,000	13,000
Neutrophils:	60%	71%
Eosinophils:	-	-
Lymphocytes:	32%	22%
Monocytes :	8%	7%

CASE 28

This patient was admitted to hospital for treatment of otitis externa. On admission, the temperature was already elevated and the patient complained of headache which had commenced that day. On the 5th. day of fever a maculo-papular rash appeared on the trunk and upper limbs, and a harsh, irritating cough made its appearance. The following day the spleen was palpable one fingerbreadth below the costal margin and the liver was just palpable. The inguinal glands were slightly enlarged. Cerebration was slow.

Epistaxis occurred on the 8th. day and the cough had become more pronounced, though the temperature was now beginning to fall. Crepitations could be heard on inspiration and expiration at the base of the left lung, but there was no limitation of movement, alteration of vocal fremitus or resonance, of the percussion note or of the breath sounds.

During the course of the next 3 days the pulmonary condition cleared up entirely and defervescence took place. Convalescence was uninterrupted.

Weil-Felix reaction:

	8th. day	11th. day
Proteus OXK	0	1/320
Proteus OX19	0	0
Proteus OX2	0	0

CASE 29

Admitted on the 2nd. day of illness, the patient complained of headache, feverishness, and discomfort in the abdomen.

The face was flushed. There was no eschar or rash, and the liver and spleen were not palpable. The cervical glands were slightly enlarged. Though there was no cough some rhonchi were audible on the left side of the chest.

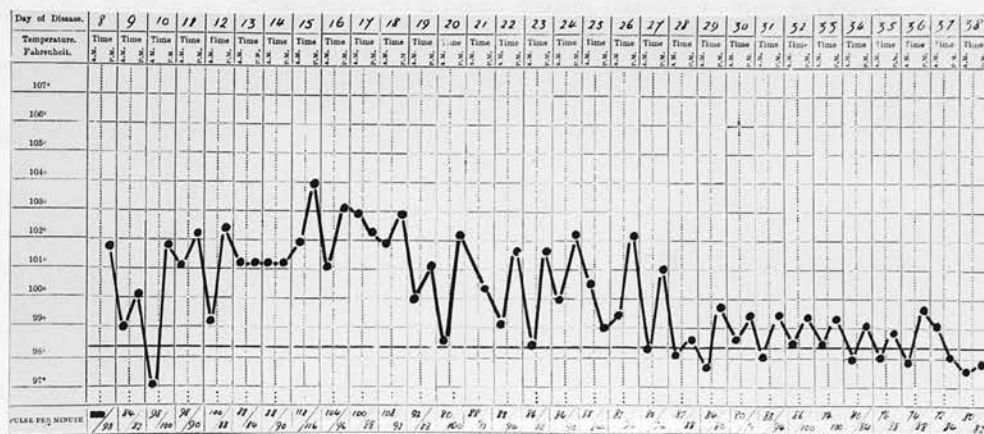
By the 5th. day the liver and spleen were both just palpable. There was now a slight cough.

By the 8th. day the cough had become more frequent and irritating, and fine crepitations were detected at both pulmonary bases. The rhonchi had also increased, but no other physical signs were detected in the lungs. These manifestations gradually decreased from the 10th. day onwards, and with complete defervescence on the 17th. day, they had quite disappeared.

Weil-Felix reaction:

	7th. day	18th. day
Proteus OXK	1/80	1/640
Proteus OX19	1/20	1/20
Proteus OX2	0	0

CASE 30



This patient was admitted on the 8th. day, complaining of headache and feverishness. The face was flushed and there was a slight icteric tinge in the conjunctivae. No rash was present, there was no eschar, the lymph glands were not enlarged and the liver and spleen were not palpable. There were no further developments till the 12th. day, when the cervical, axillary and inguinal glands were found to be enlarged.

On the 23rd. day the slight cough which the patient had had since the beginning of the illness became worse, and there was pain on breathing on the right side of the chest. Examination revealed the presence of fine crepitations at the right base. No alterations were detected in lung resonance or in the breath sounds. On the following day the percussion note was slightly impaired and the crepitations had increased. In addition, there were now a few crepitations at the left base, though there was no dulness. X-ray examination showed "haziness at the right base suggesting pneumonia".

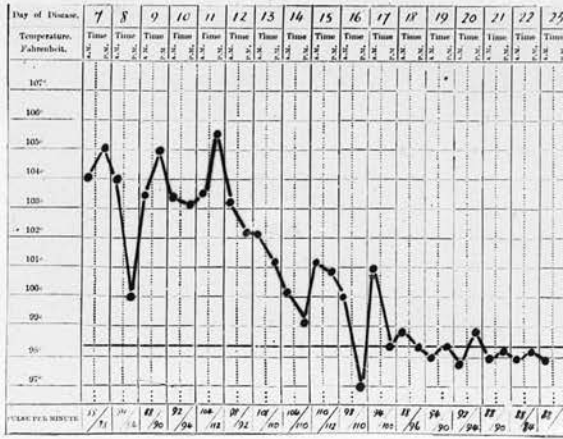
This pulmonary condition, which amounted, in terms of physical signs, to the presence of crepitations at both lung bases and some impairment of the

percussion note at the right base, persisted unchanged for 4 days. The condition then began to clear up. After a further 4 days the respiratory system was normal on physical examination.

On the 29th. day of the illness saphenous thrombosis occurred in the right leg. There was much oedema, which began to subside by the 37th. day. Convalescence was protracted, the long fever and the complications having left the patient in a weak state, but a good recovery was ultimately made.

Weil-Felix reaction:

	12th. day	19th. day	24th. day
Proteus OXK	0	1/80	1/320
Proteus OX19	0	0	0
Proteus OX2	0	0	0

CASE 31

Admitted on the 7th. day, the patient complained of headache, and had vomited frequently during the first three days of his illness. He had also had epistaxis twice, and was very constipated.

On examination, the patient was rather apathetic. The face was flushed and the conjunctivae were suffused. Two eschars were present, one on the left thigh and the other on the right anterior axillary fold. The axillary and inguinal glands were enlarged. A maculopapular rash was present on the trunk and upper limbs. The liver and spleen were not palpable.

A cough, frequent, irritating and unproductive, was present, and examination of the respiratory system showed the signs of acute bronchitis.

A rise of temperature on the 11th. day was accompanied by an increase in respiratory rate from the previous regular 24 per minute to a rate of 32 to 36, and the pulse rate also increased. Respiration was now becoming embarrassed and cyanosis appeared. Examination of the lungs showed the signs of patchy consolidation at the right mid-zone. No diminution of movement was noted, but vocal fremitus and vocal resonance were slightly increased, the percussion note was

impaired and the breath sounds were bronchial in character. In cultures of the sputum non-haemolytic streptococci predominated. No pneumococci were isolated.

The bronchopneumonia was treated with sulphapyridine, to which it responded rapidly. During the course of treatment with this drug the cyanosis increased, though the use of oxygen had at first much diminished it. It yielded, however, to the exhibition of methylene blue gr. iii b.i.d. for 2 days. During convalescence there was tachycardia and the patient complained of occasional palpitations. Full recovery, though slow, was uneventful.

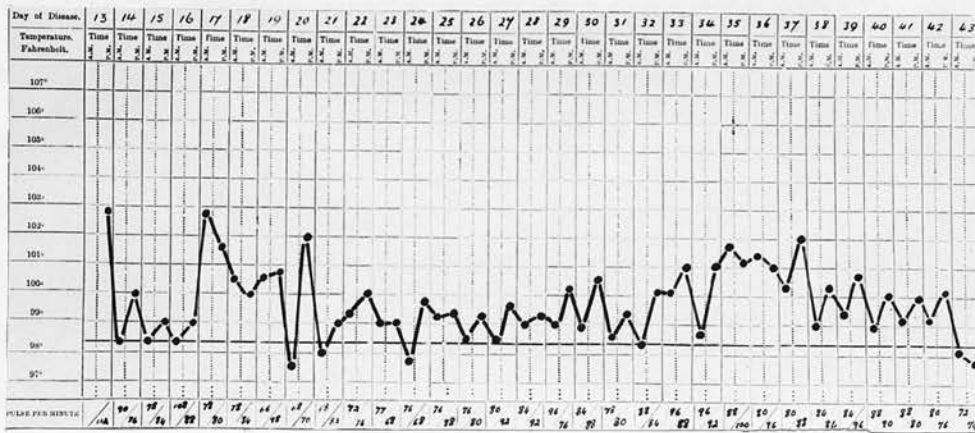
Weil-Felix reaction:

	8th. day	16th. day
Proteus OXK	0	1/160
Proteus OX19	0	0
Proteus OX2	0	0

Blood examination:

	7th. day	15th. day
W.b.c.	: 6,000	24,000
Neutrophils:	57%	52%
Eosinophils:	-	1%
Lymphocytes:	34%	43%
Monocytes :	9%	4%

CASE 32



Admitted on the 13th. day, the patient complained of headache, backache and pains in the limbs, cough and sore throat.

On examination, the face was slightly flushed and the conjunctivae were suffused. There was no rash, nor had one been observed previously. Two eschars were present, one on the back of the neck and one on the left calf. The cervical, axillary and inguinal glands were enlarged but the liver and spleen were both not palpable. No abnormalities were found in the respiratory system, apart from the cough.

The fever pursued an irregular course, and on the 22nd. day, when it appeared as if the temperature might be about to settle, a boil appeared on the neck. The spleen was now palpable one fingerbreadth below the costal margin. The organ continued to enlarge and on the 26th. day it extended 4 fingerbreadths below the costal margin and was tender. The temperature had meanwhile been rising gradually, but by the 30th. day appeared to be tending towards normal again. But the spleen had steadily increased in size and now extended a handsbreadth below the costal margin. The temperature had once more begun to increase, and by the 37th.

day had reached its acme.

The spleen now extended below the umbilicus, was hard on palpation, but was much less tender. The abdominal wall had meanwhile become reddened, and despite the fact that tenderness had recently decreased, it was apparent that surgical intervention would be necessary. Accordingly, aspiration was performed but blood and splenic tissue only were withdrawn. The symptoms did not abate as a result of this procedure, though the temperature dropped to a somewhat lower level. Seven days later - on the 42nd, day of the illness - the abdominal wall was incised and a drain inserted into the abdominal abscess, which communicated with the spleen. Much pus was obtained, direct films of which showed numerous pus cells and Gram-positive cocci in groups, and cultures gave a pure and abundant growth of a haemolytic *Staph. aureus*.

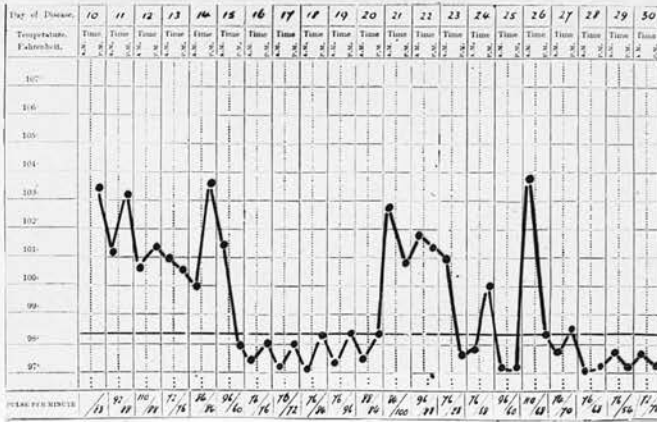
The temperature dropped to normal the following day, and though the subsequent convalescence was slow, the patient made a remarkably good recovery.

Weil-Felix reaction:

	15th. day	20th. day
Proteus OXK	1/80	1/320
Proteus OX19	0	0
Proteus OX2	0	0

Blood examination:

	20th. day	36th. day
W.b.c. :	8,000	14,000
Neutrophils:	70%	82%
Eosinophils:	3%	3%
Lymphocytes:	20%	14%
Monocytes :	7%	1%

CASE 33

This patient was admitted on the 10th. day of his attack of mite borne typhus, complaining of severe headache, and backache.

On examination, the face was flushed and the conjunctivae were suffused. No eschar was present and there had been no rash. The liver was just palpable and the spleen extended one fingerbreadth below the costal margin. The axillary glands were enlarged.

The temperature returned to normal by crisis on the 15th. day, and remained so for 5 more days. Fever then commenced once more, and after some preliminary irregularity, assumed at the 4th. day a tertian form. As with all the cases in this series, repeated blood slides had been examined on admission, but no malaria parasites had been found. In view of the recrudescence of pyrexia the blood was again examined and ring forms of *P. vivax* were found on the 6th. day of renewed fever, not having been found in examinations made during the two previous days. Appropriate treatment was instituted and the temperature fell forthwith. There was epistaxis on the last day of fever. Recovery was uneventful.

Weil-Felix reaction:

	11th. day	17th. day
Proteus OXK	1/80	1/640
Proteus OX19	0	0
Proteus OX2	0	0

CASE 34

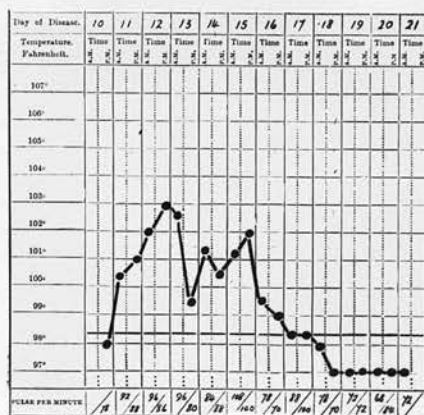
This patient was admitted on the 5th. day of illness, complaining of severe headache and pains in the small of the back and limbs. The diagnosis of malignant tertian malaria had been made elsewhere, and there had been no response to treatment. The patient was admitted to hospital for further investigation and treatment.

On examination, the face was flushed and the conjunctivae were suffused. The spleen was just palpable and the axillary glands were slightly enlarged. There was no eschar or rash. No malaria parasites were found in the blood.

The course of anti-malaria treatment which had been commenced before the patient's admission to hospital was completed. There was no apparent effect on the course of the mite borne typhus infection. Convalescence and recovery ensued in the usual manner.

Weil-Felix reaction:

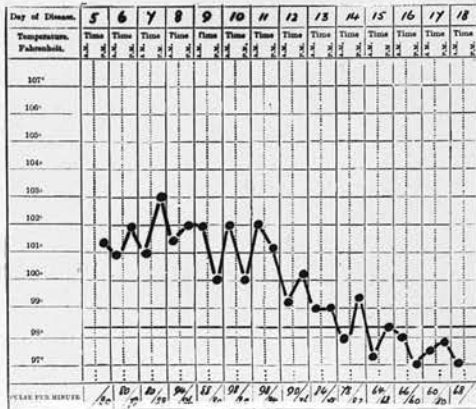
	8th. day	14th. day	21st. day
Proteus OXK	0	1/40	1/320
Proteus OX19	0	0	0
Proteus OX2	0	0	0

CASE 35

This is rather a mild case of mite borne typhus, complicated by benign tertian malaria. The malarial infection, discovered on the patient's admission to hospital on the 10th. day, did not appear to influence the course of the mite borne typhus in any way. The clinical features were headache, an eschar on the right thigh and enlargement of the cervical and inguinal glands. The spleen was palpable one fingerbreadth below the costal margin. There was no rash.

Weil-Felix reaction:

	10th. day	18th. day
Proteus OXK	0	1/320
Proteus OX19	0	0
Proteus OX2	0	0

CASE 36

Admitted on the 5th. day, there was complaint of headache and constipation.

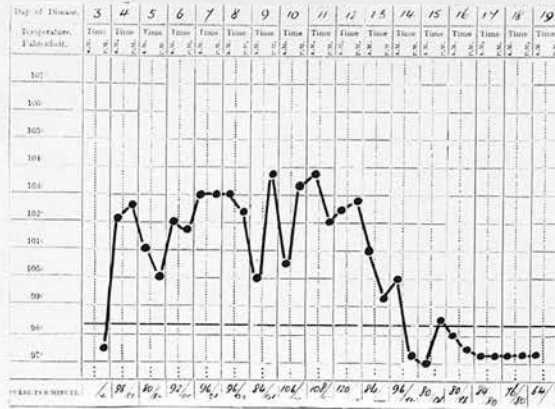
On examination, the face was flushed and the conjunctivae were suffused. An eschar was present on the back, at the waist level, and the cervical, axillary and inguinal glands were enlarged. The liver and spleen were barely palpable. The rash appeared on the 6th. day, affecting the trunk only. Rings and trophozoites of *P. vivax* were found in the blood.

The temperature continued to rise till the 7th. day, remained between 100 deg. and 102 deg. F. till the 11th. day by which time the rash had almost disappeared, and then descended by lysis. Mentally, the patient was rather dull throughout the course of the disease.

Weil-Felix reaction:

10th. day

Proteus OXK	1/320
Proteus OX19	0
Proteus OX2	0

CASE 37

The patient was admitted on the 3rd. day of the disease complaining of headache, pains in the back, slight cough and slight sore throat.

On examination there was a well-marked macular rash on the trunk. The palms and soles were deep red in colour but showed no macules or papules. There was congestion of the fauces and some slight oedema of the uvula, but no membrane or pus formation was present. Swabs were negative for *C. diphtheriae*. Examination of the respiratory system revealed the presence of acute bronchitis. Trophozoites of *P. vivax* were present in the blood.

There was no eschar, the liver and spleen were not palpable and there was no lymphadenopathy. The patient sweated freely and there was a peculiar mousy odour associated with this.

The rash began to fade in 3 to 4 days and by the 9th. day had quite disappeared from the body but had now appeared, and was well-marked, on the palms and soles. The headache had become progressively worse, and on the 11th. day lumbar puncture was performed. This measure relieved the headache temporarily.

Performed again 3 days later, the headache was permanently relieved. This coincided with defervescence, however.

Weil-Felix reaction:

	12th. day	19th. day
Proteus OXK	1/320	1/2,560
Proteus OX19	0	0
Proteus OX2	0	0

CASE 38

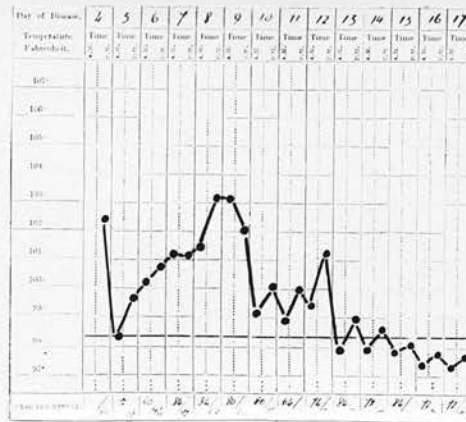
In this case the complicating malaria was of the malignant tertian variety.

The manifestations of mite borne typhus were scanty. The patient was admitted on the 5th. day of illness, complaining of headache. The face was flushed and there was enlargement of the axillary and inguinal glands. The spleen extended 2 fingerbreadths below the costal margin. Rings of *P.falciparum* were found in the blood.

Here again the malarial infection appeared not to have influenced the course of the mite borne typhus infection in any way.

Weil-Felix reaction:

	10th. day
Proteus OXK	1/640
Proteus OX19	0
Proteus OX2	0

Case 39

Admitted on the 4th. day, the patient complained of headache.

The only abnormality found on physical examination was enlargement of the spleen, the organ extending 3 fingerbreadths below the costal margin. Blood films showed ring forms of *P.vivax*.

Treatment was commenced and the temperature fell to normal by the following morning. The temperature rose again in the afternoon however, and remained elevated for the next 5 days.

Since intermissions such as that which occurred on the 5th. day occur also in uncomplicated mite borne typhus, it is not possible to impute the intermission in this case to the effect of anti-malaria treatment. However, the steady rise of temperature from the 5th. day onward suggests that this represents the actual invasion period of mite borne typhus, the pyrexia previous to this having been purely malarial. It is also interesting to note that this is an example of atypical mite borne typhus. The diagnosis would have been very difficult to make without serological tests.

Weil-Felix reaction:

	6th. day	11th. day
Proteus OXK	1/80	1/320
Proteus OX19	0	0
Proteus OX2	0	0

Case 40.

This patient had a typical attack of mite borne typhus complicated by benign tertian malaria. He was admitted to hospital on the 4th. day of illness, complaining of headache, slight diarrhoea and cough.

On examination, the cervical and axillary glands were found to be enlarged, and the spleen extended one fingerbreadth below the costal margin. Blood films showed the presence of rings and trophozoites of *P.vivax*. On the 6th. day a scanty maculo-papular rash appeared on the trunk, proximal portions of the limbs and also on the face. The inguinal glands had now enlarged, but the cough had almost disappeared.

The concurrent malaria infection appeared in no way to influence the course of the mite borne typhus. During convalescence there was some degree of tachycardia which lasted for about 10 days, and the patient also complained of palpitations.

Weil-Felix reaction:

	8th. day	14th. day
Proteus OXK	0	1/320
Proteus OX19	0	0
Proteus OX2	0	0

SECTION VIII

TREATMENT

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TREATMENT

Preventive Methods

Methods of prevention may be listed as follows:-

1. Avoidance, or treatment of, endemic areas.
2. Wearing of preventive clothing.
3. Use of larval repellents or larvicides.
4. Vaccination.

Endemic Areas

Individuals may be able to avoid areas where the disease is known to occur or which seem likely to be endemic. Where localities known to be infected do have to be occupied certain precautions should be taken. The ground should be burned so as to kill grass and scrub, and those removing the burnt or partly burnt vegetation should wear gauntlets. Bodies of rats killed during the burning operations should be buried. Labourers and other workers should not be permitted to sleep on the ground.

Preventive Clothing

Nagayo (1923) describes specially made mite-proof suits which have been used in the endemic areas in Japan, apparently with success. They are, however, unsuitable for routine use by agricultural and other labourers in hot and humid climates.

So far as Europeans are concerned, the customary dress in the tropics, short-sleeved shirt and shorts,

is unsuitable. The shirt sleeves should always be rolled down and long trousers should be worn, the ends being tucked into the socks or secured with puttees.

Larval Repellents and Larvicides

Kawamura (1926) found that spraying the soil with 1 in 100 petroleum emulsion killed all mites on the surface of the soil, and those buried to a depth of not more than 2 inches. When the larvae were attached to human beings he found that application of lysol was the best method of destruction.

The recently employed compounds of dibutyl phthalate type are very powerful insecticides and have the great advantage of requiring comparatively infrequent application. Doubtless reagents of this type will be tried as acarine larvicides.

Vaccines

Much experimental work on vaccines has been carried out in connection with louse borne typhus, and various methods of preparing immunising agents have been elaborated. Some of these methods have also been used in the case of mite borne typhus while others have not yet been so applied. It may be of some interest, therefore, to give a brief account of the methods of vaccine preparation in louse borne typhus, and to indicate where these methods have been applied in the case of the mite type.

Vaccines of three main types have been used in louse borne typhus. These have been composed of:-

1. Fully virulent living organisms in small doses.

2. Living organisms of attenuated virulence.

3. Killed organisms.

A brief consideration of these three types of vaccines now follows. For fuller details, the comprehensive article by Murgatroyd (1940), from which these notes have been largely compiled, should be consulted.

1. Living Organisms of full virulence.

In the case of *R. prowazeki*, Nicolle (1916) showed that by centrifugation of infected blood to varying degrees its virulence could be adjusted, since the infected agent is connected with the cellular elements while the immune bodies are contained in the plasma. Thus by altering the proportion of cells to plasma, doses of graduated virus content could be prepared.

Sparrow (1924) used varying dilutions of infected guineapig brain in which the titre of the virus tends to be constant.

Both these methods have been found to be troublesome in preparation and certainly not without danger. Accordingly, *R. mooseri* has been used in place of *R. prowazeki* since the disease it produces (flea borne typhus) is very much milder than louse borne typhus, and there is a considerable, though not complete, cross-immunity between the two organisms.

In the case of mite borne typhus, Kawamura et al. (1937, 1939) used the Pescadores strain of *R. orientalis* as a vaccine, since this strain is naturally of low virulence to man. A mild illness was produced, followed by immunity to a highly virulent strain.

2. Attenuated vaccines.

i) Biliated vaccines.

Blanc et al. (1933, 1934) used a strain of *R. mooseri* attenuated in virulence by treatment with ox bile. This treatment is believed to leave unaltered the capacity of the virus to stimulate antibody formation, while at the same time it becomes incapable of producing an active infection. Nor can the attenuated virus produce foci of typhus infection, since fleas or lice are said to be incapable of being infected by the vaccinated, whose infections remain constantly inapparent and benign.

ii) Dried coated vaccines.

Nicolle and Laigret (1935, 1936) prepared vaccines of *R. mooseri*, attenuating the organism by drying, and delaying its absorption by coating with egg yolk and oil.

Lewthwaite (1939) has attempted immunisation of guineapigs with egg yolk and olive oil coated suspensions of *R. orientalis*, but without success.

3. Killed vaccines.

i) Louse vaccines.

Da Rocha-Lima (1918) found that repeated injection of guineapigs with phenolized suspensions of lice infected with *R. prowazeki* produced a certain amount of immunity. Weigl (1930) infected lice with *R. prowazeki* per anum and allowed them to feed on immune persons. After feeding for about ten days, *R. prowazeki* in the intestines of the louse numbered from 10 to 100 millions. The intestines were then removed aseptically and emulsified in 0.5% carbolic saline. This constituted the vaccine.

ii) Mammalian tissue vaccines.

Formolized suspensions of the organs of infected laboratory animals have been used as vaccines. Zinsser and Batchelder (1930) used the exudate which forms in the tunica vaginalis in guineapigs infected with *R.mooseri*, and Zinsser and Castaneda (1931) prepared a *R.mooseri* vaccine by subjecting infected rats to X-ray treatment. By this means a richer accumulation of rickettsiae were obtained in the peritoneal exudate.

Castaneda (1939) showed that intranasal instillation of *R.mooseri* into rats produces a pneumonia, with abundant growth of rickettsiae. The richest accumulation of organisms was found in white mice (Durand and Sparrow, 1940). By grinding up the lungs and differential centrifugation a practically cell-free suspension of rickettsiae can be obtained. Suspensions of *R.prowazeki* can be obtained in a similar way if the organism contained in the ground up intestines of infected lice, is instilled intranasally into white mice. Durand and Giroud (1940) produced a formolized vaccine by this method.

iii) Tissue culture vaccines.

Nigg and Landsteiner (1932) were able to cultivate *R.prowazeki* on a medium consisting of minced guineapig tunica in serum-Tyrode solution. Kligler and Aschner (1934) prepared a formolized vaccine from such cultures.

iv) Egg culture vaccines.

Zia (1934) showed that *R.prowazeki* and *R.mooseri* grow on the chorio-allantoic membrane of the developing chick embryo, but the yields of rickettsiae

obtained by this method were insufficient for the preparation of vaccines. Cox (1938) however, showed that the rickettsiae multiply, and in large numbers, in the yolk sac of the developing chick embryo. Suspensions of the infected yolk sac are 100 to 1000 times more infective than mammalian tissue. Such material has therefore been employed in the preparation of vaccines.

Zinsser et al. (1940) have combined the yolk sac technique with the agar slant-tissue-culture method, so as to obtain a larger surface for inoculation.

In the case of *R.orientalis*, Lewthwaite (1939) has prepared vaccines of this organism by treatment of infected guineapig tissues with formalin and phenol.

The efficacy of rickettsial vaccines.

The use of living vaccines in louse borne typhus has been abandoned. On the one hand, such vaccines may produce infection in the subject of vaccination, while on the other there is evidence to show that the blood of persons who have previously had typhus fever may become virulent after these persons have been fed on by infected lice. That is to say, despite some degree of immunity, the typhus virus may persist in the body for some time and thus a focus of infection may be formed.

In the case of mite borne typhus, Kawamura's method is also open to objection on the grounds that an active infection is produced, though there is, of course, no danger of producing a focus of infection from which the disease might spread.

In louse borne typhus the use of attenuated vaccines has apparently been attended with good results in preventing the development of epidemics, but any method involving the use of living organisms is too dangerous for routine use, for reasons already given.

Killed vaccines are thus the only safe preparations for routine use. There is general agreement, however, that killed vaccines as now used do not confer complete immunity, but stimulate a substantial degree of partial immunity. Thus there are numerous reports of infection occurring in previously immunized persons (Gold and Fitzpatrick, 1942; Van den Ende et al., 1943; and others).

The earlier types of killed vaccines, those prepared from suspensions of infected mammalian tissues, were of very uncertain value. This was largely due to the fact that such tissue suspensions contained relatively small numbers of rickettsiae. Vaccines prepared by the more recent methods of yolk sac cultivation and lung infection contain much larger quantities of virus, and have given promising results. Felix (1942) however, suggests that before any killed vaccine can be of use it must contain the heat-labile antigenic component of the rickettsiae. This antigenic component, he thinks, is quite probably damaged by phenol and formalin, and this is likely to be one reason why unequivocally successful results have not hitherto been obtained. However this may be, it seems certain that the use of vaccines prepared by the usual methods, and containing large numbers of rickettsiae has at least partially solved the problem.

Killed vaccines have been used in mite borne typhus. Anigstein (1933) cultivated rickettsia-like organisms on artificial media inoculated with the blood of patients and the tissues of infected animals. Suspensions of the organism in 0.3% formalin were used as a vaccine. The results were not very clear cut, and in any case it is uncertain whether *R.orientalis* can indeed be cultivated by Anigstein's method.

Lewthwaite (1939) found that formolized and phenolized vaccines produced no real immunity to infection with *R.orientalis* in guineapigs.

No reports have yet been published on vaccines of *R.orientalis* prepared by the yolk sac infection or lung infection methods. By analogy, these would seem the most hopeful lines on which further work might be based.

Treatment of Mite Borne Typhus

There is no specific treatment for mite borne typhus. Hayashi et al. (1933) state that antisera in combination with a "certain drug" gave satisfactory results in the treatment of the tsutsugamushi disease. Lewthwaite (1939) found that the serum of a horse repeatedly injected with suspensions of *R. orientalis* failed to protect guineapigs against infection, though a slight effect was noted when the serum was concentrated.

Sulphonamides are of great value in secondary bacterial infections, but are without effect on the rickettsial infection.

Though penicillin possesses a marked inhibitory effect on the growth of *R.mooseri* in the yolk sac of

the developing chick embryo (Grieff and Pinkerton, 1944), and produced encouraging results in the treatment of mice infected with this organism (Moragues et al., 1944), this drug apparently has no effect on the course of mite borne typhus (Bulletin of the United States Army Medical Department, 1944).

The treatment of mite borne typhus thus resolves itself into the treatment of a febrile disease in the tropics, and no special mention need be made of the general principles governing such treatment. In the paragraphs which follow, however, attention is drawn to those points to which special attention should be given, mainly by reason of the fact that treatment is being carried out, in most cases, in a hot climate.

General Management

Efficient nursing is essential. Since the disease occurs in hot, humid areas, provision of cool hospital wards, air-conditioned where necessary, should be made. For the same reason, and also because there is prolonged confinement to bed, nursing care must be especially scrupulous. Pressure sores are to be guarded against, and to this end reliance should not be placed solely on rubbing with spirit and powdering, but the patient's position in bed should be frequently changed. The toilet of the mouth is another matter on which care must be expended. Parotitis has been reported in some cases.

Diet

Since the febrile period may last up to four

weeks or longer, care must be taken that the patient's nutritional requirements are fulfilled. The diet should be fluid or semi-solid and provide at least 2,400 calories per day, with 100 mgm. first class protein. Frequent small feeds should be given. An adequate fluid and salt intake is an especially important point, since sweating is a well-marked feature of the disease. At least four and a half litres of fluid are required daily. In some cases, occurring during the present conflict, very low plasma sodium chloride concentrations have been noted. The administration of sodium chloride, 10 gm. per day, is said to have effected a marked improvement in many seriously ill cases. The majority of patients could be induced to take their fluids well, sodium chloride gr. xx being added to each pint. In some cases, where drowsiness and apathy were marked, tube feeding, rectal administration or intravenous administration of fluids had to be employed.

Symptomatic Treatment

Headache

Aspirin in gr.x doses is usually sufficient to afford relief from headache. Where this symptom is more severe, lumbar puncture will probably give relief.

Insomnia.

Insomnia can be very troublesome. It usually yields to a simple sedative, such as potassium bromide and chloral hydrate, grs.xv of each. Morphia may be required.

Delirium.

Mild delirium may be controlled by the bromide and chloral hydrate mixture, with the addition of tinct. opii m. xv. If more severe, morphia gr. $\frac{1}{4}$, hyoscine hydrobromide gr. 1/200 should be given.

Treatment of ComplicationsSecondary pulmonary infection.

Sulphapyridine should be administered for secondary bacterial infection of the lungs. It should be given in the usual dosage for pneumonia.

Cyanosis requires the administration of oxygen. This should be given continuously by the B.L.B. mask.

Malaria.

A full course of anti-malaria treatment is required. It has already been emphasised that malaria must always be suspected as a possible complicating disease, since those areas in which mite borne typhus occurs are generally endemic malaria regions as well. Some authorities recommend that all cases of mite borne typhus, either suspected or definitely diagnosed as such, be given the full treatment for malaria, whether or not malaria parasites are found in the blood.

Other complications.

Parotitis, venous thrombosis, etc. are treated on the usual lines.

Conclusions

Methods of prevention of mite borne typhus are described and their relative values discussed. All have their place but the most valuable measure would

appear to be a combination of the various of larval destruction.

The efficacy of rickettsial vaccines is also discussed and it is concluded that though these, as at present used, give a substantial degree of partial immunity, they do not give complete protection. Vaccines of *R.orientalis* have proved to be completely unsuccessful, but the more efficacious methods of preparing rickettsial vaccines have not yet been applied in the case of this organism.

The curative treatment of mite borne typhus is governed by those principles which apply to the treatment of acute infective diseases generally. There is no specific remedy. In the description of the treatment emphasis has been given to those points which require special attention in the hot and humid climates in which the disease often occurs.

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